IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 7,037,917 Issued: May 2, 2006
Expiration Date: November 5, 2019

Inventors: Bart De Corte; Marc Rene De Jonge; Jan Heeres; Chih Yung Ho; Paul Adriaan Jan Janssen; Robert W. Kavash; Lucien Maria Henricus Koymans; Michael Joseph Kukla; Donald William Ludovici; Koen Jeanne Alfons Van Aken; Koenraad Jozef Lodewijk Marcel Andries

Title: HIV REPLICATION INHIBITING PYRIMIDINES

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM (37 C.F.R. § 1.740)

Pursuant to 35 U.S.C. §156(d) and 37 C.F.R. §1.740, Janssen Pharmaceutica, N.V. ("Applicant") as Assignee and patent owner of the above-captioned patent, hereby petitions for extension of U.S. Patent No. 7,037,917 (the '917 Patent). In support of such Petition, Applicant provides the following information:

I. SIGNATURE REQUIREMENTS (37 C.F.R. §1.730)

A. IDENTIFICATION OF PERSON(S) SUBMITTING THE APPLICATION

I, Laura A. Donnelly, represent that I am a registered practitioner appointed by the patent owner of record.

B. RECORDAL OF ASSIGNMENT IN PTO

This application; which was filed as U.S. Application Serial No. 10/634,682, is a continuation of U.S. Application Serial No. 09/430,966, filed November 1, 1999, which issued on April 12, 2005 as U.S. Patent No. 6,878,717, which claims priority to U.S. Application Serial No. 60/107,792, filed on November 10, 1998, U.S. Application Serial No. 60/143,962, filed on July 15, 1999, and PCT/EP99/07417, filed on September 24, 1999. Three assignment documents for U.S. Application Serial No. 09/430,966 were recorded on February 18, 2000 at Reel/Frame 010440/0410 from Bart De Corte, Chih Yung Ho, Robert W. Kavash, Michael Joseph Kukla and Donald William Ludovici to Janssen Pharmaceutica, Inc., and Reel/Frame 010441/0104 from Janssen Pharmaceutica, Inc. to Janssen Pharmaceutica, N.V., and Reel/Frame 010441/0104 from Marc Rene De Jonge, Jan Heeres; Paul Adriaan Jan Janssen, Lucien Maria Henricus Koymans, and Koen Jeanne Alfons Van Aken to Janssen Pharmaceutica, N.V. A fourth assignment document for U.S. Patent No. 7,037,917 was recorded on January 31, 2008 at Reel/Frame 020431/0958 from Koenraad Jozef Lodewijk Marcel Andries to Janssen Pharmaceutica, N.V.

C. PROOF OF AUTHORIZATION OF SIGNATORY TO ACT ON BEHALF OF THE PATENT OWNER

Attached as **Exhibit 1** is a Power of Attorney and Related Documents establishing authorization of Laura A. Donnelly to act on behalf of the patent owner.

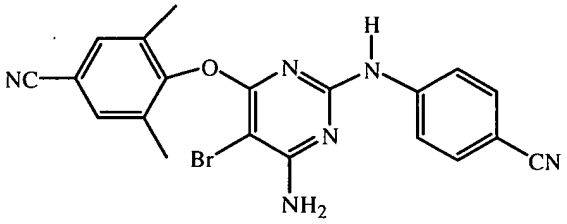
II. APPLICATION REQUIREMENTS (37 C.F.R. §1.740)

A. IDENTIFICATION OF APPROVED PRODUCT (1.740(a)(1))

The United States Food and Drug Administration ("FDA") has approved New Drug Application ("NDA") No. 22-187 for INTELENCE™ (etravirine). The active ingredient of INTELENCE™ is etravirine which is contained in the drug product as the free base form. A copy of the approved labeling is attached hereto as **Exhibit 2**.

The IUPAC (International Union of Pure and Applied Chemistry) chemical name for etravirine is 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl] amino]benzonitrile. This nomenclature was used for the compound in the '917 Patent. Another way to express the chemical name for etravirine is the CAS (Chemical Abstracts Services) name, i.e., [4-[[6-amino-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile. This nomenclature was used for the compound in the FDA documentation. The molecular formula for etravirine is $C_{20}H_{15}BrN_6O$.

Etravirine has the following structural formula:



Each tablet of INTELENCE™ contains 100 mg of etravirine.

B. IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH REGULATORY REVIEW OCCURRED (1.740(a)(2))

Regulatory review for this product occurred under the Federal Food Drug & Cosmetic Act ("FDC Act") §505(b), 21 U.S.C. §355 (new drugs).

C. DATE OF APPROVAL (1.740(a)(3))

The FDA approved NDA No. 22-187 for INTELENCE™ for commercial marketing or use under §505 of the FDC Act on January 18, 2008.

D. IDENTIFICATION OF ACTIVE INGREDIENTS AND PREVIOUS APPROVAL INFORMATION (1.740(a)(4))

INTELENCE™ is a human drug product, the sole active ingredient of which is etravirine. Neither etravirine, nor any salt or ester thereof, has been previously approved, alone or in combination, for commercial marketing or use under the Food, Drug & Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

E. TIMELY SUBMISSION OF APPLICATION (60 DAYS) (1.740(a)(5))

This application is being submitted within the sixty-day time period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last date this application may be submitted is March 18, 2008.

F. IDENTIFICATION OF PATENT (1.740(a)(6), (7), (8))

Name of the Inventors:	Bart De Corte Marc Rene De Jonge Jan Heeres Chih Yung Ho Paul Adriaan Jan Janssen Robert W. Kavash Lucien Maria Henricus Koymans Michael Joseph Kukla Donald William Ludovici Koen Jeanne Alfons Van Aken Koenraad Jozef Lodewijk Marcel Andries
Patent No.	7,037,917
Date of Issue:	May 2, 2006
Date of Original Expiration:	November 5, 2019

A copy of the patent, including the entire specification (with claims) and drawings is attached as **Exhibit 3**.

A copy of the U.S. Patent & Trademark Office Maintenance Fee Bibliographic Data is attached as **Exhibit 4**. The first maintenance fee payment is due November 3, 2009.

A terminal disclaimer pursuant to 37 C.F.R. § 1.321(a) was filed on June 9, 2005 (and refiled on August 2, 2005) in the '917 Patent disclaiming the terminal part of the statutory tem of any patent which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§ 154 and 173 of U.S. Patent 6,878,717. A copy of the disclaimers is attached as **Exhibit 5**. The '917 Patent remains commonly owned with U.S. Patent 6,878,717.

A copy of a request for certificate of correction, which was filed on January 28, 2008, is attached as **Exhibit 6**. The certificate of correction was requested by the Applicant pursuant to 35 U.S.C. § 256 to add the inventor Koenraad Jozef Lodewijk Marcel Andries.

No reexamination certificate has issued in the '917 patent.

G. IDENTIFICATION OF CLAIMS READING ON THE APPROVED PRODUCT (1.740(a)(9))

The '917 Patent claims the active ingredient of the approved Product which is etravirine as well as a method of using the approved Product. The '917 Patent includes 32 claims, of which

claims 1-5, 9, 11, 15, 21, 22, and 26-32 claim etravirine, a pharmaceutical formulation containing etravirine, a combination of etravirine and another retroviral compound, and/or the use of etravirine to treat HIV. A claim chart that lists each applicable claim of the '917 Patent and demonstrates the manner in which each claim reads on the approved Product is attached as **Exhibit 7**.

H. RELEVANT DATES AND INFORMATION (1.740(a)(10))

The '917 Patent claims a human drug.

The effective date of the investigational new drug (IND) application was December 27, 2001 and the IND No. is 63,646.

The new drug application (NDA) was initially submitted on July 17, 2007 and was received by the FDA on July 18, 2007. The NDA No. is 22-187.

The NDA was approved on January 18, 2008.

I. DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW (1.740(a)(11))

Attached as **Exhibit 8** is a "DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW" that provides a description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved Product and the significant dates applicable to such activities.

J. STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION (1.740(a)(12))

Attached as **Exhibit 9** is a "STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION AND LENGTH OF EXTENSION CLAIMED" that states that in the opinion of the applicant the '917 Patent is eligible for the extension and the length of extension claimed, including how the length of extension was determined.

K. ACKNOWLEDGEMENT OF DUTY OF DISCLOSURE (1.740(a)(13))

I, Laura A. Donnelly, the person signing below, acknowledge the duty to disclose to the Director of the U.S. Patent and Trademark Office and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension which is being sought herein.

L. FEE (1.740(a)(14))

The Application fee due is $1,120.00 (37 C.F.R. § 1.740(a)(14) and § 1.20(j)).

Authorization is hereby made to charge the amount of $1,120.00 to Deposit Account No. 10-0750/JAB1425USCNT1/LAD.

Please also charge any additional fees required by this paper or credit any overpayment to Deposit Account No. 10-0750/ JAB1425USCNT1/LAD.

M. CORRESPONDENCE

Please direct all inquiries and correspondence relating to this application to:

Philip S. Johnson, Esq.
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933

Attn: Laura Donnelly

Phone: (732) 524-1729
Facsimile: (732) 524-2808

N. COPIES (§ MPEP 2753 (8th Edition, Rev. No. 6))

Four additional copies of this application are attached, making a total of five copies being submitted.

Conclusion

In conclusion, on the basis of the information provided herein, Applicant respectfully asserts that U.S. Patent No. 7,037,917 is entitled to the requested 404 day extension of its term to December 13, 2020.

Prompt action on this application is respectfully requested.

Date: March 11, 2008

Laura A Donnelly

Signature of Practitioner

Reg. No.: 38,435
Tel. No.: 732-524-1729
Customer No.: 000027777

Laura A. Donnelly
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933
U.S.A.

Exhibit 1 **Power of Attorney and Related Documents**

PTO/SB/81 (01-06)
Approved for use through 12/31/2008. OMB 0651-0035
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY OR AUTHORIZATION OF AGENT

Patent Number	7,037,917
Issue Date	May 2, 2006
First Named Inventor	De Corte
Attorney Docket Number	JAB1425USCNT1

I hereby appoint:

☒ Practitioners at Customer Number 000027777 →

Place Customer Number Bar Code Label Here

OR

☐ Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to transact all business in the United States Patent and Trademark Office connected therewith.

Please change the correspondence address for the above-identified application to:
☒ The above-mentioned Customer Number.

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☐ Firm or Individual Name					
Address					
Address					
City		State		Zip	
Country					
Telephone		Fax			

I am the:
☐ Applicant/Inventor

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

SIGNATURE of Applicant or Assignee of Record

Name	Frank Daelemans
Signature	F. Daelemans
Date	17 Dec 2007

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

JAB1425USCNT1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 7,037,917

Issued : May 2, 2006

For : HIV REPLICATION INHIBITING PYRIMIDINES

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE UNDER 37 CFR 3.73(b)

Janssen Pharmaceutica, N.V., a Corporation, certifies that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application identified above. The assignment was recorded in the Patent and Trademark Office at Reel , Frame , or for which a copy thereof is attached.

OR

B. ☒ A chain of title as shown below:

Three assignment documents for U.S. Application Serial No. 09/430,966, a parent application to the application that issued as the above-identified patent, were recorded in the U.S. Patent Office as follows:

1. From: Bart De Corte, Chih Yung Ho, Robert W. Kavash, Michael Joseph Kukla and Donald William Ludovici
   To: Janssen Pharmaceutica, Inc.

   The document was recorded in the Patent and Trademark Office on February 18, 2000 at Reel 010440, Frame 0410, or for which a copy thereof is attached.

2. From: Janssen Pharmaceutica, Inc.
   To: Janssen Pharmaceutica, N.V.
   The document was recorded in the Patent and Trademark Office on February 18, 2000 at Reel

011516, Frame 0718, or for which a copy thereof is attached.

3. From: Marc Rene De Jonge, Jan Heeres; Paul Adriaan Jan Janssen, Lucien Maria Henricus Koymans, and Koen Jeanne Alfons Van Aken
To: Janssen Pharmaceutica, N.V.
The document was recorded in the Patent and Trademark Office on February 18, 2000 at Reel 010441, Frame 0103, or for which a copy thereof is attached.

A fourth assignment document was submitted after issuance of the above-identified patent and has been submitted to the U.S. Patent Office.

4. From: Koenraad Jozef, Lodewijk, Marcel Andries
To: Janssen Pharmaceutica, N.V.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☒ Copies of assignments or other documents in the chain of title are attached.

The undersigned has reviewed all the documents in the chain of title of the patent application identified above and, to the best of undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to sign this certificate on behalf of the assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

17 December 2007

Date

Signature

Frank Daelemans

Typed or Printed Name

PROXY HOLDER

Title

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

500452728A

JANUARY 31, 2008

PTAS

PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 01/31/2008 REEL/FRAME: 020431/0958
NUMBER OF PAGES: 2

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: JAB-1425-USCNT1

ASSIGNOR:
ANDRIES, KOENRAAD JOZEF LODEWIJK MARCEL DOC DATE: 01/28/2008

ASSIGNEE:
JANSSEN PHARMACEUTICA N.V.
TURNHOUTSEWEG 30
BEERSE, BELGIUM B-2340

SERIAL NUMBER: 10634682 FILING DATE: 08/05/2003
PATENT NUMBER: 7037917 ISSUE DATE: 05/02/2006
TITLE: HIV REPLICATION INHIBITING PYRIMIDINES

ASSIGNMENT SERVICES BRANCH
PUBLIC RECORDS DIVISION

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

01/31/2008
500452728

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
Koenraad Jozef Lodewijk Marcel Andries	01/28/2008

RECEIVING PARTY DATA

Name:	Janssen Pharmaceutica N.V.
Street Address:	Turnhoutseweg 30
City:	Beerse
State/Country:	BELGIUM
Postal Code:	B-2340

PROPERTY NUMBERS Total: 1

Property Type	Number
Patent Number:	7037917

CORRESPONDENCE DATA

Fax Number: (732)524-2808
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 7325241760
Email: Kkingsbu@corus.jnj.com
Correspondent Name: Philip S. Johnson
Address Line 1: Johnson & Johnson
Address Line 2: One Johnson & Johnson Plaza
Address Line 4: New Brunswick, NEW JERSEY 08933

ATTORNEY DOCKET NUMBER:	JAB-1425-USCNT1
NAME OF SUBMITTER:	Kristine Kingsbury

Total Attachments: 1
source=Assignment (Andries to Janssen)#page1.tif

CH $40.00 7037917

UNITED STATES PATENT AND TRADEMARK OFFICE

Facsimile Transmission

To:	**Name:**	PHILIP S. JOHNSON
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	Voice Phone:	571-272-3350

37 C.F.R. 1.6 sets forth the types of correspondence that can be communicated to the Patent and Trademark Office via facsimile transmissions. Applicants are advised to use the certificate of facsimile transmission procedures when submitting a reply to a non-final or final Office action by facsimile (37 CFR 1.8(a)).

Fax Notes:

Pg#	Description
1	Cover Page
2	437.TXT
4	Document 1, Batch 1161939

USPTO ASSIGNMENT SYSTEM PROCESSING

Date and time of transmission: Friday, February 01, 2008 3:24:10 PM
Number of pages including this cover sheet: 04

ASSIGNMENT

WHEREAS for good and valuable consideration, the receipt of which is hereby acknowledged, I, **Andries**, Koenraad Jozef Lodewijk Marcel, citizen of Belgium, residing at c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, 2340 Beerse, Belgium (hereinafter called "Assignor") sell and assign to JANSSEN PHARMACEUTICA N.V., a corporation of the State of Belgium, (hereinafter called "Assignee"), its successors and assigns, all my right, title, *and interest in and to the inventions in U.S. Patent No. 7,037,917 and all* extensions, renewals, and reissues thereof, the same to be held and enjoyed by said Assignee, its successors and assigns, as fully and entirely as the same would have been held and enjoyed by Assignors if this Assignment and sale had not been made;

The Assignor further covenants and agrees that he will, whenever requested, but without cost to him promptly communicate to said Assignee or its representatives any facts known to him relating to inventions disclosed and claimed in said patent, testify in any legal proceedings involving said inventions, and execute any additional papers that may be necessary to enable said Assignee or its representatives, successors, nominees, or assigns to secure full and complete protection for the inventions, including, if necessary, obtaining and enforcing patent protection in all countries, or that may be necessary to vest in said Assignee the complete title to the inventions and patents hereby conveyed and to enable it to record said title.

IN TESTIMONY WHEREOF, Assignor has hereunto set his hands and seals this day of January 28, 2008

.....(L.S.)-
Andries, Koenraad Jozef Lodewijk Marcel

BE IT REMEMBERED, that on this 28th day of January, 2008, before me, a Notary Public, personally appeared **Andries**, Koenraad Jozef Lodewijk Marcel who I am satisfied is the person named in and who executed the foregoing instrument in my presence, and I having first made known to him the contents thereof, he did acknowledge that he signed, sealed, and delivered the same as his voluntary act and deed for the uses and purposes therein expressed.

Notary Public

T. DOPPENS Geassocieerd Notaris - WOMMELGEM

Exhibit 2 **Approved Labeling for INTELENCE™**

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INTELENCE™ safely and effectively. See full prescribing information for INTELENCE™.

INTELENCE™ (etravirine) [Tablets]

Initial U.S. Approval – 2008

----------INDICATIONS AND USAGE----------

INTELENCE™ is a human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated:

- In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to an NNRTI and other antiretroviral agents. (1)

In patients who have experienced virologic failure on an NNRTI-containing regimen, do not use INTELENCE™ in combination with only N[t]RTIs. (1)

The safety and efficacy of INTELENCE™ have not been established in pediatric patients or treatment-naïve adult patients. (1)

----------DOSAGE AND ADMINISTRATION----------

200 mg (two 100 mg tablets) taken twice daily following a meal. (2)

----------DOSAGE FORMS AND STRENGTHS----------

100 mg tablets (3)

----------CONTRAINDICATIONS----------

None

----------WARNINGS AND PRECAUTIONS----------

Severe and potentially life threatening skin reactions, including cases of Stevens-Johnson syndrome, hypersensitivity reaction, and erythema multiforme, have been reported. Discontinue treatment if severe rash develops. (5.1)

----------ADVERSE REACTIONS----------

The most common adverse events (incidence > 10%) of any intensity that occurred at a higher rate than placebo are rash and nausea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Tibotec Therapeutics at 1-877-REACH-TT or 1-877-732-2488 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

INTELENCE™ should not be co-administered with the following antiretrovirals:

- Tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir
- Protease inhibitors administered without ritonavir
- NNRTIs

Co-administration of INTELENCE™ with drugs that inhibit or induce CYP3A4, CYP2C9, and/or CYP2C19 may alter the therapeutic effect or adverse reaction profile of INTELENCE™. (7)

Co-administration of INTELENCE™ with drugs that are substrates of CYP3A4, CYP2C9, and/or CYP2C19 may alter the therapeutic effect or adverse reaction profile of the co-administered drugs. (7)

Refer to the Full Prescribing Information for other drugs that should not be co-administered with INTELENCE™ and for other drugs that may require a change in dose or regimen. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: *Pregnancy Category B*—Use during pregnancy only if the potential benefit justifies the potential risk. Antiviral Pregnancy Registry available. Register patients by calling 1-800-258-4263. (8.1)
- Nursing Mothers: Mothers should not breastfeed due to the potential for HIV transmission. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

FULL PRESCRIBING INFORMATION: CONTENTS*

[*Sections or subsections omitted from the full prescribing information are not listed]

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INTELENCE™*, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to a non-nucleoside reverse transcriptase inhibitor (NNRTI) and other antiretroviral agents.

This indication is based on Week 24 analyses from 2 randomized, double-blind, placebo-controlled trials of INTELENCE™. Both studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, N[t]RTI, PI) treatment-experienced adults.

The following points should be considered when initiating therapy with INTELENCE™:

- Treatment history and, when available, resistance testing, should guide the use of INTELENCE™.
- The use of other active antiretroviral agents with INTELENCE™ is associated with an increased likelihood of treatment response.
- In patients who have experienced virologic failure on an NNRTI-containing regimen, do not use INTELENCE™ in combination with only N[t]RTIs [*see Clinical Studies (14)*].
- The risks and benefits of INTELENCE™ have not been established in pediatric patients or in treatment-naïve adult patients.

2 DOSAGE AND ADMINISTRATION

The recommended oral dose of INTELENCE™ tablets is 200 mg (two 100 mg tablets) taken twice daily following a meal [*see Clinical Pharmacology (12.3)*]. The type of food does not affect the exposure to etravirine. Patients who are unable to swallow INTELENCE™ tablets whole may disperse the tablets in a glass of water. Once dispersed, patients should stir the dispersion well and drink it immediately. The glass should be rinsed with water several times and each rinse completely swallowed to ensure the entire dose is consumed.

3 DOSAGE FORMS AND STRENGTHS

100 mg white to off-white oval tablets debossed with "TMC125" on one side and "100" on the other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Severe Skin Reactions

Severe and potentially life-threatening skin reactions have occurred in patients taking INTELENCE™, including Stevens-Johnson syndrome, hypersensitivity reaction, and erythema multiforme. These reactions have been reported in < 0.1% of subjects taking INTELENCE™. Treatment with INTELENCE™ should be discontinued and appropriate therapy initiated if severe rash develops.

In general, in clinical trials, rash was mild to moderate, occurred primarily in the second week of therapy and was infrequent after Week 4. Rash generally resolved within 1-2 weeks on continued therapy [*see Adverse Reactions (6)*]. A total of 2% of HIV-1-infected subjects receiving INTELENCE™ discontinued from Phase 3 trials due to rash.

* Trademark of Tibotec Pharmaceuticals Ltd.

5.2 Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including INTELENCE™. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, and tuberculosis), which may necessitate further evaluation and treatment.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety assessment is based on all data from 1203 subjects in the ongoing Phase 3 placebo-controlled trials, TMC125-C206 and TMC125-C216, conducted in antiretroviral treatment-experienced HIV-1-infected adult subjects, 599 of whom received INTELENCE™ (200 mg b.i.d.). In these pooled trials, the median exposure for subjects in the INTELENCE™ arm and placebo arm was 30.0 and 29.1 weeks, respectively.

The most commonly (> 10%) reported adverse events of all intensities and regardless of causality that occurred at a higher rate in INTELENCE™-treated subjects as compared to placebo-treated subjects are presented in Table 1.

Table 1: Adverse Events of All Intensities and Regardless of Causality at a Higher Rate Compared to Placebo in > 10% of Adult Subjects in the INTELENCE™ Treatment Groups

	Pooled TMC125-C206 and TMC125-C216 Trials	
System Organ Class, Preferred Term, %	**INTELENCE™ + BR N=599**	**Placebo + BR N=604**
Gastrointestinal Disorders		
Nausea	13.9%	11.1%
Skin and Subcutaneous Tissue Disorders		
Rash (any type)	16.9%	9.3%

N=total number of subjects per treatment group, BR=background regimen

The most frequently reported adverse drug reaction (ADR) at least Grade 2 in severity was rash (9.0%). Stevens-Johnson syndrome, hypersensitivity reaction, and erythema multiforme were reported in < 0.1% of subjects during clinical development with INTELENCE™. A total of 2% of HIV-1-infected subjects in Phase 3 trials receiving INTELENCE™ discontinued due to rash. In general, in clinical trials, rash was mild to moderate, occurred primarily in the second week of therapy, and was infrequent after Week 4. Rash generally resolved within 1-2 weeks on continued therapy [*see Warnings and Precautions (5.1)*]. The incidence of rash was higher in women compared to men in the INTELENCE™ arm. Patients with a history of NNRTI-related rash did not appear to be at increased risk for the development of INTELENCE™-related rash compared to patients without a history of NNRTI-related rash.

Common Adverse Reactions

ADRs of moderate intensity or greater (≥ Grade 2) and reported in ≥ 2% of subjects treated with INTELENCE™ are presented in Table 2. Laboratory abnormalities considered ADRs are included in Table 3.

Table 2: Treatment-Emergent Adverse Reactions* of at least Moderate Intensity† (Grades 2-4) in ≥ 2% of Adult Subjects in the INTELENCE™ Treatment Groups

System Organ Class, Preferred Term, %	Pooled TMC125-C206 and TMC125-C216 Trials	
	INTELENCE™ + BR N=599	Placebo + BR N=604
Gastrointestinal Disorders		
Diarrhea	5.2%	9.6%
Nausea	4.7%	3.5%
Abdominal pain	3.0%	2.5%
Vomiting	2.3%	2.0%
General Disorders and Administration Site Conditions		
Fatigue	3.3%	4.0%
Nervous System Disorders		
Peripheral neuropathy	2.8%	1.8%
Headache	2.7%	4.1%
Skin and Subcutaneous Tissue Disorders		
Rash	9.0%	3.1%
Vascular Disorders		
Hypertension	2.8%	2.2%

N=total number of subjects per treatment group, BR=background regimen
* Includes adverse reactions at least possibly, probably, or very likely related to the drug.
† Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).

Less Common Adverse Reactions

Treatment-emergent ADRs occurring in less than 2% of subjects (n=599) receiving INTELENCE™ and of at least moderate intensity (≥ Grade 2) are listed below by body system:

Cardiac Disorders: myocardial infarction, angina pectoris, atrial fibrillation
Ear and Labyrinth Disorders: vertigo
Eye Disorders: blurred vision
Gastrointestinal Disorders: gastroesophageal reflux disease, flatulence, gastritis, abdominal distension, pancreatitis, constipation, dry mouth, hematemesis, retching, stomatitis
General Disorders and Administration Site Conditions: sluggishness
Hematologic Disorders: anemia, hemolytic anemia
Hepatobiliary Disorders: cytolytic hepatitis, hepatic steatosis, hepatitis, hepatomegaly
Immune System Disorders: drug hypersensitivity, immune reconstitution syndrome
Metabolism and Nutrition Disorders: diabetes mellitus, dyslipidemia, anorexia
Nervous System Disorders: paraesthesia, somnolence, convulsion, hypoesthesia, syncope, amnesia, hypersomnia, tremor
Psychiatric Disorders: insomnia, anxiety, sleep disorders, abnormal dreams, confusional state, disorientation, nervousness, nightmares
Renal and Urinary Disorders: renal failure
Reproductive System and Breast Disorders: gynecomastia

Respiratory, Thoracic and Mediastinal Disorders: exertional dyspnea, bronchospasm
Skin and Subcutaneous Tissue Disorders: night sweats, hyperhidrosis, prurigo, dry skin, lipohypertrophy, swelling face

Additional ADRs of at least moderate intensity observed in other trials were acquired lipodystrophy, angioneurotic edema, erythema multiforme and haemorrhagic stroke, each reported in no more than 0.5% of subjects.

Laboratory Abnormalities in Treatment-Experienced Patients

Selected Grade 2 to Grade 4 laboratory abnormalities that represent a worsening from baseline observed in adult subjects treated with INTELENCE™ are presented in Table 3.

Table 3: Selected Grade 2 to 4 Laboratory Abnormalities Observed in Treatment-Experienced Subjects

		Pooled TMC125-C206 and TMC125-C216 Trials	
Laboratory Parameter Preferred Term, %	**DAIDS Toxicity Range**	**INTELENCE™ + BR N=599**	**Placebo + BR N=604**
GENERAL BIOCHEMISTRY			
Pancreatic amylase			
Grade 2	> 1.5-2 x ULN	5.9%	7.3%
Grade 3	> 2-5 x ULN	6.3%	7.0%
Grade 4	> 5 x ULN	1.2%	1.0%
Lipase			
Grade 2	> 1.5-3 x ULN	3.4%	4.8%
Grade 3	> 3-5 x ULN	1.7%	1.2%
Grade 4	> 5xULN	1.0%	0.5%
Creatinine			
Grade 2	> 1.4-1.8 x ULN	4.7%	4.0%
Grade 3	> 1.9-3.4 x ULN	1.9%	1.2%
Grade 4	> 3.4 x ULN	0%	0.2%
HEMATOLOGY			
Decreased hemoglobin			
Grade 2	90-99 g/L	1.9%	3.5%
Grade 3	70-89 g/L	1.0%	0.7%
Grade 4	< 70 g/L	0.7%	0.7%
Neutrophils			
Grade 2	750-999/mm^3	4.4%	5.3%
Grade 3	500-749/mm^3	2.7%	3.5%
Grade 4	< 500/mm^3	1.0%	2.8%
Platelet count			
Grade 2	50,000-99,999/mm^3	2.9%	4.5%
Grade 3	25,000-49,999/mm^3	1.2%	0.8%
Grade 4	< 25,000/mm^3	0.2%	0.2%
LIPIDS AND GLUCOSE			
Total cholesterol			
Grade 2	> 6.20-7.77 mmol/L 240-300 mg/dL	18.0%	12.6%
Grade 3	> 7.77 mmol/L > 300 mg/dL	5.8%	4.1%
Low density lipoprotein			
Grade 2	4.13-4.9 mmol/L 160-190 mg/dL	11.5%	9.1%
Grade 3	> 4.9 mmol/L	5.2%	5.4%

	> 190 mg/dL		
Triglycerides			
Grade 2	5.65-8.48 mmol/L 500 –750 mg/dL	7.1%	6.5%
Grade 3	8.49-13.56 mmol/L 751 - 1200 mg/dL	4.1%	3.0%
Grade 4	> 13.56 mmol/L > 1200 mg/dL	2.9%	1.3%
Elevated glucose levels			
Grade 2	6.95-13.88 mmol/L 161-250 mg/dL	13.1%	10.8%
Grade 3	13.89-27.75 mmol/L 251 – 500 mg/dL	2.5%	1.8%
Grade 4	> 27.75 mmol/L > 500 mg/dL	0%	0.2%
HEPATIC PARAMETERS			
Alanine amino transferase			
Grade 2	2.6-5 x ULN	5.4%	4.0%
Grade 3	5.1-10 x ULN	1.9%	1.3%
Grade 4	> 10 x ULN	0.7%	0.3%
Aspartate amino transferase			
Grade 2	2.6-5 x ULN	5.1%	6.5%
Grade 3	5.1-10 x ULN	2.0%	1.3%
Grade 4	> 10 x ULN	0.5%	0.3%
ULN=Upper Limit of Normal, BR=background regimen			

Patients co-infected with hepatitis B and/or hepatitis C virus

In Phase 3 trials TMC125-C206 and TMC125-C216, 140 subjects (12.4%) with chronic hepatitis B and/or hepatitis C virus co-infection out of 1130 subjects were permitted to enroll. AST and ALT abnormalities occurred more frequently in hepatitis B and/or hepatitis C virus co-infected subjects for both treatment groups. Grade 2 or higher laboratory abnormalities that represent a worsening from baseline of AST, ALT or total bilirubin occurred in 22.8%, 21.4% and 5.7% respectively, of INTELENCE™-treated co-infected subjects as compared to 5.5%, 6.1% and 1.2% of non-co-infected INTELENCE™-treated subjects. In general, adverse events reported by INTELENCE™-treated subjects with hepatitis B and/or hepatitis C virus co-infection were similar to INTELENCE™-treated subjects without hepatitis B and/or hepatitis C virus co-infection.

7 DRUG INTERACTIONS

Etravirine is a substrate of CYP3A4, CYP2C9, and CYP2C19. Therefore, co-administration of INTELENCE™ with drugs that induce or inhibit CYP3A4, CYP2C9, and CYP2C19 may alter the therapeutic effect or adverse reaction profile of INTELENCE™ (see Table 4). [*See also Clinical Pharmacology (12.3).*]

Etravirine is an inducer of CYP3A4 and inhibitor of CYP2C9 and CYP2C19. Therefore, co-administration of drugs that are substrates of CYP3A4, CYP2C9 and CYP2C19 with INTELENCE™ may alter the therapeutic effect or adverse reaction profile of the co-administered drug(s) (see Table 4). *[See also Drug Interactions (7) and Clinical Pharmacology (12.3).*]

Table 4 shows the established and other potentially significant drug interactions based on which, alterations in dose or regimen of INTELENCE™ and/or co-administered drug may be recommended. Drugs that are not recommended for co-administration with INTELENCE™ are also included in Table 4.

Table 4: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction
[See Clinical Pharmacology (12.3)]

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
efavirenz* nevirapine*	↓ etravirine	Combining two NNRTIs has not been shown to be beneficial. Concomitant use of INTELENCE™ with efavirenz or nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of INTELENCE™. INTELENCE™ and other NNRTIs should not be co-administered.
delavirdine	↑ etravirine	Combining two NNRTIs has not been shown to be beneficial. INTELENCE™ and delavirdine should not be co-administered.
HIV-Antiviral Agents: Protease Inhibitors (PIs)—Unboosted (i.e., without co-administration of low-dose ritonavir)		
atazanavir* fosamprenavir nelfinavir indinavir* (without ritonavir)	↓ atazanavir ↑ amprenavir ↑ nelfinavir ↓ indinavir	Concomitant use of INTELENCE™ with PIs without co-administration of low-dose ritonavir may cause a significant alteration in the plasma concentrations of the PI. INTELENCE™ should not be co-administered with PIs without low-dose ritonavir.
ritonavir*	↓ etravirine	Concomitant use of INTELENCE™ with ritonavir 600 mg b.i.d. may cause a significant decrease in the plasma concentration of etravirine and loss of therapeutic effect of INTELENCE™. INTELENCE™ and ritonavir 600 mg b.i.d. should not be co-administered.
HIV-Antiviral Agents: Protease Inhibitors (PIs)—Boosted (with co-administration of low-dose ritonavir)		
tipranavir/ritonavir*	↓ etravirine	Concomitant use of INTELENCE™ with tipranavir/ritonavir may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of INTELENCE™. INTELENCE™ and tipranavir/ritonavir should not be co-administered.
fosamprenavir/ritonavir*	↑ amprenavir	Due to a significant increase in the systemic exposure of amprenavir, the appropriate doses of the combination of INTELENCE™ and fosamprenavir/ritonavir have not been established. INTELENCE™ and fosamprenavir/ritonavir should not be co-administered.
atazanavir/ritonavir*	↓ atazanavir ↑ etravirine	Concomitant use of INTELENCE™ with atazanavir/ritonavir may cause a significant decrease in atazanavir C_{min} by about 38% and loss of therapeutic effect of atazanavir. In addition, the mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with atazanavir/ritonavir is anticipated to be about 100% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. INTELENCE™ and

		atazanavir/ritonavir should not be co-administered.
darunavir/ritonavir	↓ etravirine	The mean systemic exposure (AUC) of etravirine was reduced by about 37% when INTELENCE™ was co-administered with darunavir/ritonavir. Because all subjects in the Phase 3 trials received darunavir/ritonavir as part of the background regimen and etravirine exposures from these trials were determined to be safe and effective, INTELENCE™ and darunavir/ritonavir can be co-administered without any dose adjustments.
lopinavir/ritonavir	↑ etravirine	The mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with lopinavir/ritonavir is anticipated to be about 85% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. The amount of safety data at these increased etravirine exposures is limited, therefore, INTELENCE™ and lopinavir/ritonavir should be co-administered with caution.
saquinavir/ritonavir	↓ etravirine	The mean systemic exposure (AUC) of etravirine was reduced by about 33% when INTELENCE™ was co-administered with saquinavir/ritonavir. Because the reduction in the mean systemic exposures of etravirine in the presence of saquinavir/ritonavir is similar to the reduction in mean systemic exposures of etravirine in the presence of darunavir/ritonavir, INTELENCE™ and saquinavir/ritonavir can be co-administered without any dose adjustments.
Other Agents		
Antiarrhythmics: amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↓ antiarrhythmics	Concentrations of these antiarrhythmics may be decreased when co-administered with INTELENCE™. INTELENCE™ and antiarrhythmics should be co-administered with caution. Drug concentration monitoring is recommended, if available.
Anticoagulants: warfarin	↑ anticoagulants	Warfarin concentrations may be increased when co-administered with INTELENCE™. The international normalized ratio (INR) should be monitored when warfarin is combined with INTELENCE™.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ etravirine	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. INTELENCE™ should not be used in combination with carbamazepine, phenobarbital, or phenytoin as co-administration may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE™.
Antifungals: fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole	↑ etravirine ↔ fluconazole ↓ itraconazole ↓ ketoconazole ↔ posaconazole ↑ voriconazole	Posaconazole is a potent inhibitor of CYP3A4 and fluconazole is a potent inhibitor of CYP2C9; both may increase plasma concentrations of etravirine. Itraconazole and ketoconazole are potent inhibitors as well as substrates of CYP3A4. Concomitant systemic use of itraconazole or ketoconazole and INTELENCE™ may increase plasma concentrations of etravirine. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by INTELENCE™. Voriconazole is a CYP2C19 substrate and CYP3A4, CYP2C9 and CYP2C19 inhibitor.

		Concomitant use of voriconazole and INTELENCE™ may increase plasma concentrations of both drugs. Dose adjustments for itraconazole, ketoconazole or voriconazole may be necessary depending on other co-administered drugs.
Antiinfectives: clarithromycin*	↑ etravirine ↓ clarithromycin ↑ 14-OH-clarithromycin	Clarithromycin exposure was decreased by INTELENCE™; however, concentrations of the active metabolite, 14-hydroxy-clarithromycin, were increased. Because 14-hydroxy-clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC), overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC.
Antimycobacterials: rifampin, rifapentine	↓ etravirine	Rifampin and rifapentine are potent inducers of CYP450 enzymes. INTELENCE™ should not be used with rifampin or rifapentine as co-administration may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE™.
Antimycobacterials: rifabutin*	↓ etravirine ↓ rifabutin ↓ 25-*O*-desacetylrifabutin	If INTELENCE™ is NOT co-administered with a protease inhibitor/ritonavir, then rifabutin at a dose of 300 mg q.d. is recommended. If INTELENCE™ is co-administered with darunavir/ritonavir or saquinavir/ritonavir, then rifabutin should not be co-administered due to the potential for significant reductions in etravirine exposure.
Benzodiazepines: diazepam	↑ diazepam	Concomitant use of INTELENCE™ with diazepam may increase plasma concentrations of diazepam. A decrease in diazepam dose may be needed.
Corticosteroids: dexamethasone (systemic)	↓ etravirine	Systemic dexamethasone induces CYP3A4 and can decrease etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE™. Systemic dexamethasone should be used with caution or alternatives should be considered, particularly for long-term use.
Herbal Products: St. John's wort (*Hypericum perforatum*)	↓ etravirine	Concomitant use of INTELENCE™ with products containing St. John's wort may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE™. INTELENCE™ and products containing St. John's wort should not be co-administered.
HMG-CoA Reductase Inhibitors: atorvastatin*	↔ etravirine ↓ atorvastatin ↑ 2-OH-atorvastatin	The combination of INTELENCE™ and atorvastatin can be given without any dose adjustments, however, the dose of atorvastatin may need to be altered based on clinical response.
fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	↔ etravirine ↑ fluvastatin, ↓ lovastatin, ↔ pravastatin, ↔ rosuvastatin, ↓ simvastatin	No interaction between pravastatin, rosuvastatin and INTELENCE™ is expected. Lovastatin and simvastatin are CYP3A4 substrates and co-administration with INTELENCE™ may result in lower plasma concentrations of the HMG-CoA reductase inhibitor. Fluvastatin is metabolized by CYP2C9 and co-administration with INTELENCE™ may result in higher plasma concentrations of the HMG-CoA reductase inhibitor. Dose adjustments for these HMG-CoA reductase inhibitors may be necessary.
Immunosuppressants:	↓	INTELENCE™ and systemic immunosuppressants should be co-

cyclosporine, sirolimus, tacrolimus	immunosuppressant	administered with caution because plasma concentrations of cyclosporine, sirolimus, or tacrolimus may be affected.
Narcotic Analgesics: methadone*	↔ etravirine ↔ methadone	INTELENCE™ and methadone can be co-administered without dose adjustments, however, clinical monitoring for withdrawal symptoms is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Phosphodiesterase Type 5 (PDE-5) Inhibitors: sildenafil*, vardenafil, tadalafil	↓ sildenafil ↓ N-desmethyl-sildenafil	INTELENCE™ and sildenafil can be co-administered without dose adjustments, however, the dose of sildenafil may need to be altered based on clinical effect.
↑ = increase, ↓ = decrease, ↔ = no change * The interaction between INTELENCE™ and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.		

In addition to the drugs included in Table 4, the interaction between INTELENCE™ and the following drugs were evaluated in clinical studies and no dose adjustment is needed for either drug [*see Clinical Pharmacology (12.3)*]: didanosine, enfuvirtide, ethinylestradiol/norethindrone, omeprazole, paroxetine, raltegravir, ranitidine, and tenofovir disoproxil fumarate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

No adequate and well-controlled studies of INTELENCE™ use in pregnant women have been conducted. In addition, no pharmacokinetic studies have been conducted in pregnant patients. Animal reproduction studies in rats and rabbits at systemic exposures equivalent to those at the recommended human dose of 400 mg/day revealed no evidence of fetal harm. INTELENCE™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to INTELENCE™, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. It is not known whether etravirine is secreted in human milk. Because of both the potential for HIV transmission and the potential for adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving INTELENCE™.**

8.4 Pediatric use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric use

Clinical studies of INTELENCE™ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

No dose adjustment of INTELENCE™ is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. The pharmacokinetics of INTELENCE™ have not been evaluated in patients with severe hepatic impairment (Child-Pugh Class C).

8.7 Renal Impairment

Since the renal clearance of etravirine is negligible (< 1.2%), a decrease in total body clearance is not expected in patients with renal impairment. No dose adjustments are required in patients with renal impairment. As etravirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

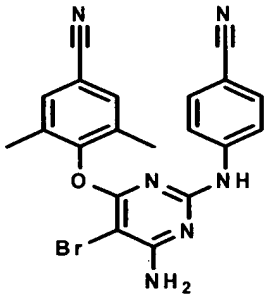
10 OVERDOSAGE

There is no specific antidote for overdose with INTELENCE™. Human experience of overdose with INTELENCE™ is limited. The highest dose studied in healthy volunteers was 400 mg once daily. Treatment of overdose with INTELENCE™ consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Because etravirine is highly protein bound, dialysis is unlikely to result in significant removal of the active substance.

11 DESCRIPTION

INTELENCE™ (etravirine) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1).

The chemical name for etravirine is 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile. Its molecular formula is $C_{20}H_{15}BrN_6O$ and its molecular weight is 435.28. Etravirine has the following structural formula:



Etravirine is a white to slightly yellowish brown powder. Etravirine is practically insoluble in water over a wide pH range. It is very slightly soluble in propylene glycol and slightly soluble in ethanol. Etravirine is soluble in polyethylene glycol (PEG)400 and freely soluble in some organic solvents (e.g., N,N-dimethylformamide and tetrahydrofuran).

INTELENCE™ is available as a white to off-white, oval tablet for oral administration containing 100 mg of etravirine. Each tablet contains the inactive ingredients hypromellose, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and lactose monohydrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Etravirine is an antiviral drug [*see Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

Effects on Electrocardiogram

In a randomized, double-blind, active, and placebo-controlled crossover study, 41 healthy subjects were administered INTELENCE™ 200 mg b.i.d., INTELENCE™ 400 mg q.d., placebo, and moxifloxacin 400 mg. After 8 days of dosing, etravirine did not prolong the QT interval. The maximum mean (upper 1-sided 95% CI) baseline and placebo-adjusted QTcF were 0.6 ms (3.3 ms) for 200 mg b.i.d. and -1.0 ms (2.5 ms) for 400 mg q.d. dosing regimens.

12.3 Pharmacokinetics

Pharmacokinetics in Adults

The pharmacokinetic properties of INTELENCE™ were determined in healthy adult subjects and in treatment-experienced HIV-1-infected adult subjects. The systemic exposures (AUC) to etravirine were lower in HIV-1-infected subjects than in healthy subjects.

Table 5: Population Pharmacokinetic Estimates of Etravirine 200 mg b.i.d. in HIV-1-Infected Subjects (Integrated Data from Phase 3 Trials at Week 24)*

Parameter	Etravirine 200 mg b.i.d. N = 574
AUC_{12h} (ng•h/mL)	
Geometric Mean ± Standard Deviation	4531.53 ± 4543.69
Median (Interquartile Range)	4450.7 (3091.3 - 6315.0)
C_{0h} (ng/mL)	
Geometric Mean ± Standard Deviation	296.74 ± 377.52
Median (Interquartile Range)	298.8 (188.5 - 462.3)

* All HIV-1-infected subjects enrolled in Phase 3 clinical trials received darunavir/ritonavir 600/100 mg b.i.d. as part of their background regimen. Therefore, the pharmacokinetic parameter estimates shown in Table 5 account for reductions in the pharmacokinetic parameters of etravirine due to co-administration of INTELENCE™ with darunavir/ritonavir.

Note: The median protein binding adjusted EC50 for MT4 cells infected with HIV-1/IIIB in vitro = 4 ng/mL.

Absorption and Bioavailability

Following oral administration, etravirine was absorbed with a T_{max} of about 2.5 to 4 hours. The absolute oral bioavailability of INTELENCE™ is unknown.

In healthy subjects, the absorption of etravirine is not affected by co-administration of oral ranitidine or omeprazole, drugs that increase gastric pH.

Effects of Food on Oral Absorption

The systemic exposure (AUC) to etravirine was decreased by about 50% when INTELENCE™ was administered under fasting conditions, as compared to when INTELENCE™ was administered following a meal. Therefore, INTELENCE™ should always be taken following a meal. Within the range of meals studied, the systemic exposures to etravirine were similar. The total caloric content of the various meals evaluated ranged from 345 kilocalories (17 grams fat) to 1160 kilocalories (70 grams fat). [*see Dosage and Administration (2)*].

Distribution

Etravirine is about 99.9% bound to plasma proteins, primarily to albumin (99.6%) and alpha 1-acid glycoprotein (97.66%-99.02%) *in vitro*. The distribution of etravirine into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Metabolism

In vitro experiments with human liver microsomes (HLMs) indicate that etravirine primarily undergoes metabolism by CYP3A4, CYP2C9, and CYP2C19 enzymes. The major metabolites, formed by methyl hydroxylation of the dimethylbenzonitrile moiety, were at least 90% less active than etravirine against wild-type HIV in cell culture.

Elimination

After single dose oral administration of 800 mg ^{14}C-etravirine, 93.7% and 1.2% of the administered dose of ^{14}C-etravirine was recovered in the feces and urine, respectively. Unchanged etravirine accounted for 81.2% to 86.4% of the administered dose in feces. Unchanged etravirine was not detected in urine. The mean (± standard deviation) terminal elimination half-life of etravirine was about 41 (± 20) hours.

Special Populations

Hepatic Impairment

Etravirine is primarily metabolized by the liver. The steady state pharmacokinetic parameters of etravirine were similar after multiple dose administration of INTELENCE™ to subjects with normal hepatic function (n = 16), mild hepatic impairment (Child-Pugh Class A, n = 8), and moderate hepatic impairment (Child-Pugh Class B, n = 8). The effect of severe hepatic impairment on the pharmacokinetics of etravirine has not been evaluated.

Hepatitis B and/or Hepatitis C Virus Co-infection

Population pharmacokinetic analysis of the TMC125-C206 and TMC125-C216 trials showed reduced clearance for etravirine in HIV-1-infected subjects with hepatitis B and/or C virus co-infection. Based upon the safety profile [*see Adverse Reactions (6)*], no dose adjustment is necessary in patients co-infected with hepatitis B and/or C virus.

Renal Impairment

The pharmacokinetics of etravirine have not been studied in patients with renal impairment. The results from a mass balance study with ^{14}C-etravirine showed that <1.2% of the administered dose of etravirine is excreted in the urine as metabolites. No unchanged drug was detected in the urine. As etravirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

Gender

No significant pharmacokinetic differences have been observed between men and women. A limited number of women were included in clinical studies.

Race

Population pharmacokinetic analysis of etravirine in HIV-infected subjects did not show an effect of race on exposure to etravirine.

Geriatric Patients

Population pharmacokinetic analysis in HIV-infected subjects showed that etravirine pharmacokinetics are not considerably different within the age range (18 to 77 years) evaluated [*see Use in Specific Populations (8.5)*].

Pediatric Patients

The pharmacokinetics of etravirine in pediatric patients have not been evaluated. Dosing recommendations for pediatric patients cannot be made due to insufficient data.

Drug Interactions

[*See also Drug Interactions (7).*]

Etravirine is a substrate of CYP3A4, CYP2C9, and CYP2C19. Therefore, co-administration of INTELENCE™ with drugs that induce or inhibit CYP3A4, CYP2C9, and CYP2C19 may alter the therapeutic effect or adverse reaction profile of INTELENCE™.

Etravirine is an inducer of CYP3A4 and inhibitor of CYP2C9 and CYP2C19. Therefore, co-administration of drugs that are substrates of CYP3A4, CYP2C9 and CYP2C19 with INTELENCE™ may alter the therapeutic effect or adverse reaction profile of the co-administered drug(s).

Drug interaction studies were performed with INTELENCE™ and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of other drugs on the AUC, C_{max}, and C_{min} values of etravirine are summarized in Table 6 (effect of other drugs on INTELENCE™). The effect of co-administration of INTELENCE™ on the AUC, C_{max}, and C_{min} values of other drugs are summarized in Table 7 (effect of INTELENCE™ on other drugs). For information regarding clinical recommendations, *see Drug Interactions (7).*

Table 6: Drug Interactions: Pharmacokinetic Parameters for Etravirine in the Presence of Co-administered Drugs

Co-administered Drug	Dose/Schedule of Co-administered Drug	N	Exposure	Mean Ratio of Etravirine Pharmacokinetic Parameters 90% CI; No Effect = 1.00		
				C_{max}	AUC	C_{min}
Co-Administration With Protease Inhibitors (PIs)						
Atazanavir	400 mg q.d.	14	↑	1.47 (1.36-1.59)	1.50 (1.41-1.59)	1.58 (1.46-1.70)
Atazanavir/ ritonavir	300/100 mg q.d.	14	↑	1.30 (1.17-1.44)	1.30 (1.18-1.44)	1.26 (1.12-1.42)
Darunavir/ ritonavir	600/100 mg b.i.d.	14	↓	0.68 (0.57-0.82)	0.63 (0.54-0.73)	0.51 (0.44-0.61)
Lopinavir/ ritonavir (soft gel capsule)	400/100 mg b.i.d.	13	↑	1.15 (0.94-1.41)	1.17 (0.96-1.43)	1.23 (0.98-1.53)
Ritonavir	600 mg b.i.d.	11	↓	0.68 (0.55-0.85)	0.54 (0.41-0.73)	N.A.
Saquinavir/ ritonavir	1000/100 mg b.i.d.	14	↓	0.63 (0.53-0.75)	0.67 (0.56-0.80)	0.71 (0.58-0.87)
Tipranavir/ ritonavir	500/200 mg b.i.d.	19	↓	0.29 (0.22-0.40)	0.24 (0.18-0.33)	0.18 (0.13-0.25)
Co-Administration With Nucleoside Reverse Transcriptase Inhibitors (NRTIs)						
Didanosine	400 mg q.d.	15	↔	1.16 (1.02-1.32)	1.11 (0.99-1.25)	1.05 (0.93-1.18)
Tenofovir disoproxil fumarate	300 mg q.d.	23	↓	0.81 (0.75-0.88)	0.81 (0.75-0.88)	0.82 (0.73-0.91)
Co-Administration With Integrase Strand Transfer Inhibitors						
Raltegravir	400 mg b.i.d.	19	↔	1.04 (0.97-1.12)	1.10 (1.03-1.16)	1.17 (1.10-1.26)
Co-Administration With Other Drugs						
Atorvastatin	40 mg q.d.	16	↔	0.97 (0.93-1.02)	1.02 (0.97-1.07)	1.10 (1.02-1.19)
Clarithromycin	500 mg b.i.d.	15	↑	1.46 (1.38-1.56)	1.42 (1.34-1.50)	1.46 (1.36-1.58)
Omeprazole	40 mg q.d.	18	↑	1.17 (0.96-1.43)	1.41 (1.22-1.62)	N.A.
Paroxetine	20 mg q.d.	16	↔	1.05 (0.96-1.15)	1.01 (0.93-1.10)	1.07 (0.98-1.17)
Ranitidine	150 mg b.i.d.	18	↓	0.94 (0.75-1.17)	0.86 (0.76-0.97)	N.A.
Rifabutin	300 mg q.d.	12	↓	0.63 (0.53-0.74)	0.63 (0.54-0.74)	0.65 (0.56-0.74)

CI = Confidence Interval; N = number of subjects with data; N.A. = not available; ↑ = increase; ↓ = decrease; ↔ = no change; q.d. = once daily; b.i.d. = twice daily

Table 7: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of INTELENCE™

Co-administered Drug	Dose/Schedule of Co-administered Drug	N	Exposure	Mean Ratio of Co-administered Drug Pharmacokinetic Parameters 90% CI; No effect = 1.00		
				C_{max}	AUC	C_{min}
Co-Administration With Protease Inhibitors (PIs)						
Atazanavir	400 mg q.d.	14	↓	0.97 (0.73-1.29)	0.83 (0.63-1.09)	0.53 (0.38-0.73)
Atazanavir/ ritonavir	300/100 mg q.d.	13	↓	0.97 (0.89-1.05)	0.86 (0.79-0.93)	0.62 (0.55-0.71)
Darunavir/ ritonavir	600/100 mg b.i.d.	15	↔	1.11 (1.01-1.22)	1.15 (1.05-1.26)	1.02 (0.90-1.17)
Fosamprenavir/ ritonavir	700/100 mg b.i.d.	8	↑	1.62 (1.47-1.79)	1.69 (1.53-1.86)	1.77 (1.39-2.25)
Lopinavir/ ritonavir (soft gel capsule)	400/100 mg b.i.d.	14	↓	0.85 (0.62-1.05)	0.80 (0.49-1.07)	0.92 (0.15-1.68)
Saquinavir/ ritonavir	1000/100 mg b.i.d.	15	↔	1.00 (0.70-1.42)	0.95 (0.64-1.42)	0.80 (0.46-1.38)
Tipranavir/ ritonavir	500/200 mg b.i.d.	19	↑	1.14 (1.02-1.27)	1.18 (1.03-1.36)	1.24 (0.96-1.59)
Co-Administration With Nucleoside Reverse Transcriptase Inhibitors (NRTIs)						
Didanosine	400 mg q.d.	14	↔	0.91 (0.58-1.42)	0.99 (0.79-1.25)	N.A.
Tenofovir disoproxil fumarate	300 mg q.d.	19	↔	1.15 (1.04-1.27)	1.15 (1.09-1.21)	1.19 (1.13-1.26)
Co-Administration With Integrase Strand Transfer Inhibitors						
Raltegravir	400 mg b.i.d.	19	↓	0.89 (0.68-1.15)	0.90 (0.68-1.18)	0.66 (0.34-1.26)

Co-Administration With Other Drugs						
Atorvastatin	40 mg q.d.	16	↓	1.04 (0.84-1.30)	0.63 (0.58-0.68)	N.A.
2-hydroxy-atorvastatin		16	↑	1.76 (1.60-1.94)	1.27 (1.19-1.36)	N.A.
Clarithromycin	500 mg b.i.d.	15	↓	0.66 (0.57-0.77)	0.61 (0.53-0.69)	0.47 (0.38-0.57)
14-hydroxy-clarithromycin		15	↑	1.33 (1.13-1.56)	1.21 (1.05-1.39)	1.05 (0.90-1.22)
Ethinylestradiol	0.035 mg q.d.	16	↑	1.33 (1.21-1.46)	1.22 (1.13-1.31)	1.09 (1.01-1.18)
Norethindrone	1 mg q.d.	16	↔	1.05 (0.98-1.12)	0.95 (0.90-0.99)	0.78 (0.68-0.90)
R(-) Methadone	Individual dose regimen ranging from 60 to 130 mg/day	16	↔	1.02 (0.96-1.09)	1.06 (0.99-1.13)	1.10 (1.02-1.19)
S(+) Methadone		16	↔	0.89 (0.83-0.97)	0.89 (0.82-0.96)	0.89 (0.81-0.98)
Paroxetine	20 mg q.d.	16	↔	1.06 (0.95-1.20)	1.03 (0.90-1.18)	0.87 (0.75-1.02)
Rifabutin	300 mg q.d.	12	↓	0.90 (0.78-1.03)	0.83 (0.75-0.94)	0.76 (0.66-0.87)
25-*O*-desacetylrifabutin	300 mg q.d.	12	↓	0.85 (0.72-1.00)	0.83 (0.74-0.92)	0.78 (0.70-0.87)
Sildenafil	50 mg single dose	15	↓	0.55 (0.40-0.75)	0.43 (0.36-0.51)	N.A.
N-desmethyl-sildenafil		15	↓	0.75 (0.59-0.96)	0.59 (0.52-0.68)	N.A.

CI = Confidence Interval; N = number of subjects with data; N.A. = not available; ↑ = increase; ↓ = decrease; ↔ = no change; q.d. = once daily ; b.i.d. = twice daily

12.4 Microbiology

Mechanism of Action

Etravirine is an NNRTI of human immunodeficiency virus type 1 (HIV-1). Etravirine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. Etravirine does not inhibit the human DNA polymerases α, β, and γ.

Antiviral Activity in Cell Culture

Etravirine exhibited activity against laboratory strains and clinical isolates of wild-type HIV-1 in acutely infected T-cell lines, human peripheral blood mononuclear cells, and human monocytes/macrophages with median EC_{50} values ranging from 0.9 to 5.5 nM (i.e., 0.4 to 2.4 ng/mL). Etravirine demonstrated antiviral activity in cell culture against a broad panel of HIV-1 group M isolates (subtype A, B, C, D, E, F, G) with EC_{50} values ranging from 0.29 to 1.65 nM and EC_{50} values ranging from 11.5 to 21.7 nM against group O primary isolates. Etravirine did not show antagonism when studied in combination with the following antiretroviral drugs—the NNRTIs delavirdine, efavirenz, and nevirapine; the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir; and the fusion inhibitor enfuvirtide (ENF).

Resistance

In Cell Culture

Etravirine-resistant strains were selected in cell culture originating from wild-type HIV-1 of different origins and subtypes, as well as NNRTI resistant HIV-1. Development of reduced susceptibility to etravirine typically required more than one substitution in reverse transcriptase of which the following were observed most frequently: L100I, E138K, E138G, V179I, Y181C, and M230I.

In Treatment-Experienced Subjects

In the Phase 3 trials TMC125-C206 and TMC125-C216, substitutions that developed most commonly in subjects with virologic failure at Week 24 to the INTELENCE™-containing regimen were V179F, V179I, Y181C, and Y181I which usually emerged in a background of multiple other NNRTI resistance-associated substitutions. In all the trials conducted with INTELENCE™ in HIV-1 infected subjects, the following substitutions emerged most commonly: L100I, E138G, V179F, V179I, Y181C and H221Y. Other NNRTI-resistance associated substitutions which emerged on etravirine treatment in < 10% of the virologic failure isolates included K101E, K103N, V106I/M, V108I, Y188L, V189I, G190S/C and R356K. The emergence of NNRTI substitutions on etravirine treatment contributed to decreased susceptibility to etravirine with a median fold-change in etravirine susceptibility of 40-fold from reference and a median fold-change of 6-fold from baseline.

Cross-Resistance

Site-Directed NNRTI Mutant Virus

Etravirine showed antiviral activity against 55 of 65 HIV-1 strains (85%) with single amino acid substitutions at RT positions associated with NNRTI resistance, including the most commonly found K103N. The single amino acid substitutions associated with an etravirine reduction in susceptibility > 3-fold were K101A, K101P, K101Q, E138G, E138Q, Y181C, Y181I, Y181T, Y181V, and M230L, and of these, the greatest reductions were Y181I (13-fold change in EC_{50} value) and Y181V (17-fold change in EC_{50} value). Mutant strains containing a single NNRTI resistance associated substitution (K101P, K101Q, E138Q, or M230L) had cross-resistance between etravirine and efavirenz. The majority (39 of 61; 64%) of the NNRTI mutant viruses with 2 or 3 amino acid substitutions associated with NNRTI resistance had decreased susceptibility to etravirine (fold-change > 3). The highest levels of resistance to etravirine were observed for HIV-1 harboring a combination of substitutions V179F + Y181C (187 fold-change), V179F + Y181I (123 fold-change), or V179F + Y181C + F227C (888 fold-change).

Clinical Isolates

Etravirine retained a fold-change ≤ 3 against 60% of 6171 NNRTI-resistant clinical isolates. In the same panel, the proportion of clinical isolates resistant to delavirdine, efavirenz and/or nevirapine (defined as a fold-change above their respective biological cutoff values in the assay) was 79%, 87%, and 95%, respectively. In TMC125-C206 and TMC125-C216, 35% of the baseline isolates had decreased susceptibility to etravirine (fold-change > 3) and 61%, 71%, and 79% of these isolates were resistant to delavirdine, efavirenz, and nevirapine, respectively. Cross-resistance to delavirdine, efavirenz, and/or nevirapine is expected after virologic failure with an etravirine-containing regimen for the virologic failure isolates.

Baseline Genotype/Phenotype and Virologic Outcome Analyses

In TMC125-C206 and TMC125-C216, the presence at baseline of the substitutions V179D, V179F, V179T, Y181V, or G190S was associated with a decreased virologic response to etravirine. The presence of K103N, which was the most prevalent NNRTI substitution in TMC125-C206 and TMC125-C216 at baseline, did not affect the response in the INTELENCE™ arm. Response rates to etravirine decreased as the number of baseline NNRTI mutations increased. The presence at baseline of 3 or more IAS-USA-defined NNRTI substitutions (2007) resulted in a decreased virologic response to INTELENCE™ (shown as the proportion of subjects achieving viral load < 50 plasma HIV RNA copies/mL at Week 24) (Table 8).

Table 8: Proportion of Subjects with < 50 HIV-1 RNA copies/mL at Week 24 by Baseline Number of IAS-USA-Defined NNRTI Mutations in the As-Treated Population of Pooled TMC125-C206 and TMC125-C216 Trials

# IAS-USA-Defined NNRTI*	Etravirine Arms N = 565	
	Re-Used/Not Used ENF	De Novo ENF
All ranges	60% (251/420)	70% (102/145)
0 - 2	66% (213/322)	76% (80/105)
≥ 3	39% (38/98)	55% (22/40)
	Placebo Arms N = 593	
All ranges	34% (149/434)	62% (99/159)

* 2007 IAS-USA defined mutations = V90I, A98G, L100I, K101E/P, K103N, V106A/I/M, V108I, V179D/F, Y181C/I/V, Y188C/H/L, G190A/S, P225H

Response rates assessed by baseline etravirine phenotype are shown in Table 9. These baseline phenotype groups are based on the select subject populations in TMC125-C206 and TMC125-C216 and are not meant to represent definitive clinical susceptibility breakpoints for INTELENCE™. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to etravirine in treatment-experienced patients.

Table 9: Proportion of Subjects with < 50 HIV-1 RNA copies/mL at Week 24 by Baseline Phenotype and ENF Use in the Pooled TMC125-C206 and TMC125-C216 Trials*

Etravirine Fold Change	Etravirine Arms N = 561		
	Re-Used/Not Used ENF	De Novo ENF	Clinical Response Range
All ranges	60% (249/416)	70% (102/145)	Overall Response
0 - 3	70% (190/273)	82% (75/92)	Higher than Overall Response
> 3 - 13	47% (37/78)	50% (19/38)	Lower than Overall Response
> 13	34% (22/65)	53% (8/15)	Lower than Overall Response
	Placebo Arms N = 593		
All ranges	34% (149/434)	62% (99/159)	

* As-treated analysis

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Carcinogenicity studies of etravirine in rodents are ongoing. Etravirine tested negative in the *in vitro* Ames reverse mutation assay, *in vitro* chromosomal aberration assay in human lymphocyte, and *in vitro* clastogenicity mouse lymphoma assay, tested in the absence and presence of a metabolic activation system. Etravirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice. [*See Nonclinical Toxicology (13.2).*]

Impairment of Fertility

No effects on fertility and early embryonic development were observed when etravirine was tested in rats at maternal doses up to 500 mg/kg/day, resulting in systemic drug exposure up to the recommended human dose (400 mg/day).

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

Developmental toxicity studies were performed in rabbits (at oral doses up to 375 mg/kg/day) and rats (at oral doses up to 1000 mg/kg/day). In both species, no treatment-related embryo-fetal effects including malformations were observed. In addition, no treatment-related effects were observed in a separate pre- and postnatal study performed in rats at oral doses up to 500 mg/kg/day. The systemic drug exposures achieved in these animal studies were equivalent to those at the recommended human dose (400 mg/day).

14 CLINICAL STUDIES

14.1 Treatment-Experienced Subjects

The clinical efficacy of INTELENCE™ is derived from the analyses of 24-week data from 2 ongoing, randomized, double-blinded, placebo-controlled, Phase 3 trials, TMC125-C206 and TMC125-C216 (DUET-1 and DUET-2). These trials are identical in design and the results below are pooled data from the two trials.

TMC125-C206 and TMC125-C216 are Phase 3 studies designed to evaluate the safety and antiretroviral activity of INTELENCE™ in combination with a background regimen (BR) as compared to placebo in combination with a BR. Eligible subjects were treatment-experienced HIV-1-infected patients with plasma HIV-1 RNA > 5000 copies/mL while on a stable antiretroviral regimen for at least 8 weeks. In addition, subjects had 1 or more NNRTI resistance-associated mutations at screening or from prior genotypic analysis, and 3 or more of the following primary PI mutations at screening: D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, V82A/F/L/S/T, I84V, N88S, or L90M. Randomization was stratified by the intended use of enfuvirtide (ENF) in the BR, previous use of darunavir/ritonavir (DRV/rtv), and screening viral load. Virologic response was defined as undetectable viral load (< 50 HIV-1 RNA copies/mL) at 24 weeks.

All study subjects received DRV/rtv as part of their BR, and at least 2 other investigator-selected antiretroviral drugs (N[t]RTIs with or without ENF). Of INTELENCE™-treated subjects, 25.5% used ENF for the first time (*de novo*) and 20.0% re-used ENF. Of placebo-treated subjects, 26.5% used *de novo* ENF and 20.4% re-used ENF.

In the pooled analysis for TMC125-C206 and TMC125-C216, demographics and baseline characteristics were balanced between the INTELENCE™ arm and the placebo arm. Table 10 displays selected demographic and baseline disease characteristics of the subjects in the INTELENCE™ and placebo arms.

Table 10: Demographic and Baseline Disease Characteristics of Subjects in the TMC125-C206 and TMC125-C216 Trials (Pooled Analysis)		
	Pooled TMC125-C206 and TMC125-C216 Trials	
	INTELENCE™ + BR N=599	Placebo + BR N=604
Demographic Characteristics		
Median Age, years (range)	46 (18-77)	45 (18-72)
Sex		
Male	90.0%	88.6%
Female	10.0%	11.4%
Race		
White	70.1%	69.8%
Black	13.2%	13.0%
Hispanic	11.3%	12.2%
Asian	1.3%	0.6%
Other	4.1%	4.5%
Baseline Disease Characteristics		
Median Baseline Plasma HIV-1 RNA (range), $\log_{10}$ copies/mL	4.8 (2.7-6.8)	4.8 (2.2-6.5)
Percentage of Subjects with Baseline Viral Load:		
< 30,000 copies/mL	27.5%	28.8%
≥ 30,000 copies/mL and < 100,000 copies/mL	34.4%	35.3%
≥ 100,000 copies/mL	38.1%	35.9%
Median Baseline CD4+ Cell Count (range), cells/mm^3	99 (1-789)	109 (0-912)
Percentage of Subjects with Baseline CD4+ Cell Count:		
< 50 cells/mm^3	35.6%	34.7%
≥ 50 cells/mm^3 and < 200 cells/mm^3	34.8%	34.5%
≥ 200 cells/mm^3	29.6%	30.8%
Median (range) Number of Primary PI Mutations*	4 (0-7)	4 (0-7)
Percentage of Subjects with Previous Use of NNRTIs:		
0	8.2%	7.9%
1	46.9%	46.7%
>1	44.9%	45.4%
Percentage of Subjects with Previous Use of the following NNRTIs:		
Efavirenz	70.3%	72.5%
Nevirapine	57.1%	58.6%
Delavirdine	13.7%	12.7%
Median (range) Number of NNRTI RAMs†	2 (0-5)	2 (0-4)
Median Fold Change of the Virus for the Following NNRTIs:		
Delavirdine	27.4	26.4
Efavirenz	63.9	46.1
Etravirine	1.6	1.5
Nevirapine	74.3	74.3
Percentage of Subjects with Previous		

Use of Enfuvirtide	39.6%	41.9%

RAMs = Resistance-Associated Mutations, BR=background regimen
FC = fold change in EC_{50}
*IAS-USA primary PI mutations [November 2005]: D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, V82A/F/L/S/T, I84V, N88S, L90M
†Tibotec NNRTI RAMs [March 2007]: A98G, L100I, K101E/P/Q, K103H/N/S/T, V106A/M, V108I, E138G/K/Q, V179D/E/F/G/I, Y181C/I/V, Y188C/H/L, G190A/C/E/Q/S, H221Y, P225H, F227C/L, M230I/L, P236L, K238N/T, Y318F

Efficacy at Week 24 for subjects in the INTELENCE™ and placebo arms for the pooled TMC125-C206 and TMC125-C216 study populations are shown in Table 11.

Table 11: Outcomes of Treatment at Week 24 of the TMC125-C206 and TMC125-C216 Trials (Pooled Analysis)

	Pooled TMC125-C206 and TMC125-C216 Trials	
	INTELENCE™ + BR N=599	**Placebo + BR N=604**
Virologic Responders at Week 24 Viral Load < 50 HIV-1 RNA copies/mL	358 (59.8%)	243 (40.2%)
Virologic Failures (VF) at Week 24 Viral Load ≥ 50 HIV-1 RNA copies/mL	190 (31.7%)	320 (53.0%)
Death*	9 (1.5%)	16 (2.6%)
Discontinuations before Week 24†:		
due to VF	2 (0.3%)	3 (0.5%)
due to Adverse Events	28 (4.7%)	11 (1.8%)
due to other reasons	12 (2.0%)	11 (1.8%)

* all deaths, including the follow-up period
† all discontinuations up to and including day 154 of the treatment period
BR=background regimen

At Week 24, 74.0% of INTELENCE™-treated subjects achieved HIV-1 RNA < 400 copies/mL as compared to 51.5% of placebo-treated subjects. The mean decrease in plasma HIV-1 RNA from baseline to Week 24 was -2.37 $\log_{10}$ copies/mL for INTELENCE™-treated subjects and -1.68 $\log_{10}$ copies/mL for placebo-treated subjects. The mean CD4+ cell count increase from baseline for INTELENCE™-treated subjects was 81 cells/mm^3 and 64 cells/mm^3 for placebo-treated subjects.

Of the study population who either re-used or did not use ENF, 56.7% of INTELENCE™-treated subjects and 32.7% of placebo-treated subjects achieved HIV-1 RNA < 50 copies/mL. Of the study population using ENF *de novo,* 68.6% of INTELENCE™-treated subjects and 61.3% of placebo-treated subjects achieved HIV-1 RNA < 50 copies/mL.

Study TMC125-C227 was a randomized, exploratory, active-controlled, open-label, Phase 2b trial. Eligible subjects were treatment-experienced, PI-naïve HIV-1-infected patients with genotypic evidence of NNRTI resistance at screening or from prior genotypic analysis. The virologic response was evaluated in 116 subjects who were randomized to INTELENCE™ (n=59) or an investigator-selected PI (n=57), each given with 2 investigator-selected N(t)RTIs. INTELENCE™-treated subjects had lower antiviral responses associated with reduced susceptibility to the N(t)RTIs and to INTELENCE™ as compared to the control PI-treated subjects.

16 HOW SUPPLIED/STORAGE AND HANDLING

INTELENCE™ tablets are supplied as white to off-white, oval tablets containing 100 mg of etravirine. Each tablet is debossed with "TMC125" on one side and "100" on the other side.

INTELENCE™ tablets are packaged in bottles in the following configuration: 100 mg tablets—bottles of 120 (NDC 59676-570-01). Each bottle contains 3 desiccant pouches.

Store INTELENCE™ tablets at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature]. Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant pouches.

17 PATIENT COUNSELING INFORMATION

[See FDA-approved patient labeling].

A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with INTELENCE™ from your healthcare provider.** A Patient Package Insert for INTELENCE™ is available for patient information.

Patients should be informed that INTELENCE™ is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of INTELENCE™ are unknown at this time. Patients should be informed that INTELENCE™ does not reduce the risk of passing HIV to others through sexual contact, sharing needles, or being exposed to blood. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should also be advised to never re-use or share needles. Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using INTELENCE™.

Patients should be advised to take INTELENCE™ following a meal twice a day as prescribed. The type of food does not affect the exposure to etravirine. Patients should be instructed to swallow the tablets as a whole with a liquid such as water. Patients who are unable to swallow the INTELENCE™ tablets whole may disperse the tablets in a glass of water. Once dispersed, patients should stir the dispersion well, and drink it immediately. The glass should be rinsed with water several times, and each rinse completely swallowed to ensure the entire dose is consumed. INTELENCE™ must always be used in combination with other antiretroviral drugs. Patients should not alter the dose of INTELENCE™ or discontinue therapy with INTELENCE™ without consulting their physician. If the patient misses a dose of INTELENCE™ within 6 hours of the time it is usually taken, the patient should be told to take INTELENCE™ following a meal as soon as possible, and then take the next dose of INTELENCE™ at the regularly scheduled time. If a patient misses a dose of INTELENCE™ by more than 6 hours of the time it is usually taken, the patient should be told not to take the missed dose and simply resume the usual dosing schedule. Inform the patient that he or she should not take more or less than the prescribed dose of INTELENCE™ at any one time.

INTELENCE™ may interact with many drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort.

Severe and potentially life-threatening rash has been reported with INTELENCE™. Treatment with INTELENCE™ should be discontinued if severe rash develops. Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including INTELENCE™, and that the cause and long-term health effects of these conditions are not known at this time.

Manufactured for Tibotec, Inc. by:
Janssen Cilag S.p.A., Latina, Italy
Distributed by:
Tibotec Therapeutics, Division of Ortho Biotech Products, L.P., Raritan NJ 08869

Patent Numbers: 6,878,717 and 7,037,917; and other U.S. patents pending.

Issued January 2008

10095300

FDA-approved patient labeling

Patient Information
INTELENCE™* (in-tel-ence)
etravirine (et-ra-vir-een)
Tablets

Important: Ask your doctor or pharmacist about medicines that should NOT be taken with INTELENCE™. For more information, read the section "Can INTELENCE™ be taken with other medicines?".

Read this information carefully before you start taking INTELENCE™ and each time you renew your prescription, as new information may be available. This leaflet does not take the place of talking with your doctor. You and your doctor should discuss your treatment with INTELENCE™ when you start taking it and at regular checkups. You should not change or stop treatment without first talking with your doctor.

What is INTELENCE™?

- **INTELENCE™ is a prescription anti-HIV medicine that helps to control HIV (Human Immunodeficiency Virus) infection in adults. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).** INTELENCE™ is a type of anti-HIV medicine called a non-nucleoside reverse transcriptase inhibitor (NNRTI).
- INTELENCE™ is used with other anti-HIV medicines in patients who are already taking or have taken anti-HIV medicines and the medicines are not controlling their HIV infection.
- The long-term effects of INTELENCE™ are not known at this time. It is important that you remain under the care of your doctor during treatment with INTELENCE™.
- The safety and effectiveness of INTELENCE™ have not been studied in children.

INTELENCE™ must be taken in combination with other anti-HIV medicines.

How does INTELENCE™ work?

- INTELENCE™ blocks an enzyme which the virus (HIV) needs in order to make more virus. The enzyme that INTELENCE™ blocks is called HIV reverse transcriptase.
- When used with other anti-HIV medicines, INTELENCE™ may:
  - reduce the amount of HIV in your blood. This is called your "viral load".
  - increase the number of white blood cells called CD4+ (T) cells that help fight off other infections.

  Reducing the amount of HIV and increasing the CD4+ (T) cell count may improve your immune system and, as a result, reduce the risk of death or infections that can happen when your immune system is weak (opportunistic infections).

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Does INTELENCE™ cure HIV or AIDS?

No. INTELENCE™ does not cure HIV infection or AIDS. Right now, there is no cure for HIV infection. People taking INTELENCE™ may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak. Some of the other conditions that can happen with HIV are: pneumonia, herpes virus infection, *Mycobacterium avium* complex (MAC) infections.

Does INTELENCE™ reduce the risk of passing HIV to others?

No. INTELENCE™ does **not** reduce the risk of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood.

- Always practice safer sex.
- Use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- Never re-use or share needles.

Ask your doctor if you have any questions on how to prevent passing HIV to other people.

What should I tell my doctor before I take INTELENCE™?

Together with your doctor, you need to decide whether taking INTELENCE™ is right for you.

Tell your doctor about all of your medical conditions, including if you:

- have had or currently have liver problems, including hepatitis B or C.
- are pregnant or planning to become pregnant. It is not known if INTELENCE™ can harm your unborn baby. You and your doctor will need to decide if taking INTELENCE™ is right for you. If you take INTELENCE™ while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.
- are breastfeeding. Do not breastfeed if you are taking INTELENCE™. You should not breastfeed if you have HIV because of the chance of passing HIV to your baby. Talk with your doctor about the best way to feed your baby.

Can INTELENCE™ be taken with other medicines?**

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements, including St. John's wort (*Hypericum perforatum*). **Some medicines may interact with INTELENCE™.**

- Sometimes serious side effects happen if INTELENCE™ is taken with some medicines.
- INTELENCE™ should not be taken with some medicines which may lower the amount of INTELENCE™ in your blood. This may lead to an increased HIV viral load. Resistance to INTELENCE™ or cross resistance to other HIV medicines may develop.

** The brands listed are the registered trademarks of their respective owners and are not trademarks of Tibotec Pharmaceuticals Ltd.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine. Your doctor and your pharmacist can tell you if you can take these medicines with INTELENCE™. Do not start any new medicines while you are taking INTELENCE™ without first talking with your doctor or pharmacist. You can ask your doctor or pharmacist for a list of medicines that can interact with INTELENCE™.

Tell your doctor if you take other HIV medicines. INTELENCE™ can be combined with most HIV medicines while some HIV medicines are not recommended.

Tell your doctor if you are taking any of the following medicines:

Type of Drug	Examples of Generic Names (Brand Names)
Antiarrhythmics (to treat abnormal heart rhythms)	amiodarone (Cordarone®) bepridil (Vascor®) disopyramide (Norpace®) flecainide (Tambocor™) lidocaine (Xylocaine®) mexiletine (Mexitil®) propafenone (Rythmol SR®) quinidine (Quinidex®)
Anticoagulants (to prevent blood clots)	warfarin (Coumadin®)
Anticonvulsants (to treat epilepsy and prevent seizures)	carbamazepine (Tegretol®, Carbatrol®) phenobarbital (Luminal®) phenytoin (Dilantin®, Phenytek®)
Antifungals (to treat fungal infections)	fluconazole (Diflucan®) itraconazole (Sporanox®) ketoconazole (Nizoral®) posaconazole (Noxafil®) voriconazole (Vfend®)
Anti-infectives (to treat bacterial infections)	clarithromycin (Biaxin®)
Antimycobacterials (to treat bacterial infections, including tuberculosis (TB))	rifabutin (Mycobutin®) rifampin (Rifadin®, Rifater®, Rifamate®) rifapentine (Priftin®)
Benzodiazepines (to treat trouble with sleeping and/or anxiety)	diazepam (Valium®)
Corticosteroids	dexamethasone (Decadron®)

Type of Drug (to treat inflammation or asthma)	Examples of Generic Names (Brand Names)
HMG-CoA Reductase Inhibitors (to lower cholesterol levels)	atorvastatin (Lipitor®) fluvastatin (Lescol®) lovastatin (Advicor®, Altoprev®, Mevacor®) rosuvastatin (Crestor®) simvastatin (Vytorin®, Zocor®)
Immunosuppressants	cyclosporine (Sandimmune®, Neoral®) sirolimus (Rapamune®) tacrolimus (Prograf®)
Narcotic Analgesic	methadone (Dolophine®)
PDE-5 Inhibitors (to treat erectile dysfunction)	sildenafil (Viagra®) vardenafil (Levitra®) tadalafil (Cialis®)

This is **not** a complete list of medicines that you should tell your doctor about. Know and keep track of all the medicines you take and have a list of them with you. Show this list to all of your doctors and pharmacists any time you get a new medicine. Both your doctor and your pharmacist can tell you if you can take these other medicines with INTELENCE™.

How should I take INTELENCE™?

- **Take INTELENCE™ tablets every day exactly as prescribed by your doctor.** The usual dose is two tablets of INTELENCE™ two times each day (a total of four tablets each day). It may be easier to remember to take INTELENCE™ if you take it at the same time every day. If you have questions about when to take INTELENCE™, your doctor can help you decide which schedule works for you.

- **Take INTELENCE following a meal**. Do not take INTELENCE™ on an empty stomach. INTELENCE™ may not work as well if you take it on an empty stomach. The type of food is not important.

- Swallow INTELENCE™ tablets whole, with a liquid such as water. **Do not chew the tablets.** If you are unable to swallow the INTELENCE™ tablets whole, you may place the tablets in a glass of water. Stir well until the water looks milky, then drink it immediately. Rinse the glass with water several times, and completely swallow the rinse each time to make sure you take the entire dose.

- Do not change your dose or stop taking INTELENCE™ without first talking with your doctor. See your doctor regularly while taking INTELENCE™.

- Take all your anti-HIV medicines as prescribed and at the right times of day. This can help your medicines work better and lowers the chance that your medicines will stop working to fight HIV (drug resistance).

- When your supply of INTELENCE™ starts to run low, get more from your doctor or pharmacy. It is important not to run out of INTELENCE™. The amount of HIV in your blood may increase if the medicine is stopped even for a short time.

- If you miss a dose of INTELENCE™ within 6 hours of the time you usually take it, take your dose of INTELENCE™ following a meal as soon as possible. Then, take your next dose of INTELENCE™ at the regularly scheduled time. If you miss a dose of INTELENCE™ by more than 6 hours of the time you usually take it, wait and then take the next dose of INTELENCE™ at the regularly scheduled time.

- Do not double the next dose to make up for a missed dose. Do not take more or less than your prescribed dose of INTELENCE™ at any one time. Always take INTELENCE™ following a meal.

- If you take too much INTELENCE™, contact your local poison control center or emergency room right away.

What are the possible side effects of INTELENCE™?

Skin rash is a common side effect of INTELENCE™. Rash can be serious and potentially life-threatening, and sometimes INTELENCE™ must be stopped. Tell your doctor right away if you get a rash.

Other common side effects of INTELENCE™ include diarrhea, nausea, abdominal pain, vomiting, tiredness, tingling or pain in hands or feet, numbness, headache, and high blood pressure.

As with other anti-HIV medicines, INTELENCE™ may cause side effects, including:

- changes in body shape or body fat. These changes can happen in patients taking anti-HIV medicine. The changes may include an increased amount of fat in the upper back and neck, breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The exact cause and long term health effects of these conditions are not known.
- immune reconstitution syndrome. A condition called Immune Reconstitution Syndrome can happen in some patients with advanced HIV infection (AIDS) when HIV treatment is started. Signs and symptoms of inflammation from opportunistic infections that a person has or had may occur as the medicines work to control the HIV infection and strengthen the immune system. Call your doctor right away if you notice any signs or symptoms of an infection after starting INTELENCE™ with other anti-HIV medicines.

Tell your doctor right away about these or any other unusual symptoms. If the condition does not go away or worsens, get medical help.

These are not all of the possible side effects with INTELENCE™. For more information, ask your doctor or pharmacist.

How should I store INTELENCE™ tablets?

- Store INTELENCE™ tablets at room temperature between 59°F to 86°F (15°C to 30°C).
- Keep INTELENCE™ in the bottle given to you by your pharmacist.

Keep the bottle tightly closed to protect INTELENCE™ from moisture. The bottle contains 3 little pouches of drying agent (desiccants) to keep the tablets dry. Keep the pouches in the bottle. **Do not eat the pouches. Keep INTELENCE™ and all medicines out of the reach of children.**

General Advice about INTELENCE™

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use INTELENCE™ for a condition for which it was not prescribed. Do not give INTELENCE™ to other people even if they have the same condition you have. It may harm them.

This leaflet provides a summary of the most important information about INTELENCE™. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about INTELENCE™ that is written for health professionals. For more information, you may also call Tibotec Therapeutics at 1-877-REACH-TT or 1-877-732-2488.

What are the ingredients in INTELENCE™?

Active ingredient: Each tablet contains 100 mg of etravirine.

Inactive ingredients: hypromellose, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and lactose monohydrate

tibotec
THERAPEUTICS

Manufactured for Tibotec, Inc. by:
Janssen Cilag S.p.A., Latina, IT
Distributed by:
Tibotec Therapeutics, Division of Ortho Biotech Products, L.P., Raritan NJ 08869

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Exhibit 3 **Copy of U.S. Patent No. 7,037,917**

US006878717B2

(12) **United States Patent**
De Corte et al.

(10) **Patent No.: US 6,878,717 B2**
(45) **Date of Patent: Apr. 12, 2005**

(54) **HIV REPLICATION INHIBITING PYRIMIDINES**

(76) Inventors: **Bart De Corte**, 1590 Winding Rd., Southampton, PA (US) 18966; **Marc Rene De Jonge**, Hontenissestraat 3, 5045 CA Tilburg (NL); **Jan Heeres**, Leemskuilen 18, Vosselaar (BE), B-2350; **Chih Yung Ho**, 600 Drinnon Way, Lansdale, PA (US) 19446; **Paul Adriaan Jan Janssen**, Antwerpsesteenweg 20, B2350 Vosselaar (BE); **Robert W. Kavash**, 148 N. Keswick Ave., Maple Glen, PA (US) 19002; **Lucien Maria Henricus Koymans**, Stationstraat 68 bus 4, B-2300 Turnhout (BE); **Michael Joseph Kukla**, 1551 Oak Hollow Dr., Maple Glen, PA (US) 19002; **Donald William Ludovici**, 1390 Masi Rd., Quakertown, PA (US) 18951; **Koen Jeanne Alfons Van Aken**, Tuinbouwstraat 22, bus 2, B-2300 Turnhout (BE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 4 days.

(21) Appl. No.: **09/430,966**

(22) Filed: **Nov. 1, 1999**

(65) **Prior Publication Data**

US 2003/0114472 A1 Jun. 19, 2003

Related U.S. Application Data

(60) Provisional application No. 60/143,962, filed on Jul. 15, 1999, and provisional application No. 60/107,792, filed on Nov. 10, 1998.

(30) **Foreign Application Priority Data**

Sep. 24, 1999 (WO) ..... PCT/EP 99/07417

(51) **Int. Cl.**[7] **A61K 31/506**; A61P 31/18; C07D 239/42; C07D 239/48; C07D 239/50

(52) **U.S. Cl.** **514/269**; 514/272; 544/295; 544/296; 544/315; 544/316; 544/322; 544/323; 544/324

(58) **Field of Search** 544/295, 296, 544/315, 316, 322, 323, 324; 514/269, 272

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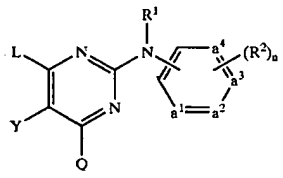
(Continued)

Primary Examiner—Richard L. Raymond
Assistant Examiner—Venkataraman Balasubramanian

(57) **ABSTRACT**

This invention concerns the use of compounds of formula:

(I)



the N-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein $-a^1=-a^2-a^3=a^4-$ forms a phenyl, pyridinyl, pyrimidinyl, pyridazinyl or pyrazinyl with the attached vinyl group; n is 0 to 4; and where possible 5; R^1 is hydrogen, aryl, formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, substituted C_{1-6}alkyl, or substituted C_{1-6}alkyloxyC_{1-6}alkylcarbonyl; each R^2 independently is hydroxy, halo, optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalo-methylthio, —S(=O)$_p$R^6, —NH—S(=O)$_p$R^6, —C(=O)R^6, —NHC(=O)H, —C(=O)NHNH$_2$, —NHC(=O)R^6, —C(=NH)R^6 or a 5-membered heterocyclic ring; p is 1 or 2; L is optionally substituted C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl or C_{3-7}cycloalkyl; or L is —X—R^3 wherein R^3 is optionally substituted phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; X is —NR^1—, —NH—NH—, —N=N—, —O—, —C(=O)—, —CHOH—, —S—, —S(=O)— or —S(=O)$_2$—; Q is hydrogen, C_{1-6}alkyl, halo, polyhalo-C_{1-6}alkyl or an optionally substituted amino group; Y represents hydroxy, halo, C_{3-7}cycloalkyl, optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, —S(=O)$_p$R^6, —NH—S(=O)$_p$R^6, —C(=O)R^6, —NHC(=O)H, —C(=O)NHNH$_2$, —NHC(=O)R^6, —C(=NH)R^6 or aryl; aryl is optionally substituted phenyl; Het is an optionally substituted heterocyclic radical; for the manufacture of a medicine for the treatment of subjects suffering from HIV (Human Immunodeficiency Virus) infection.

5 Claims, No Drawings

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HIV REPLICATION INHIBITING PYRIMIDINES

CROSS REFERENCE TO RELATED APPLICATIONS

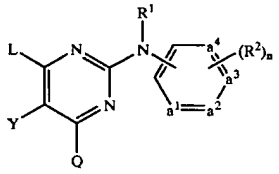
This application claims priority from U.S. provisional applications Ser. Nos. 60/107,792, filed Nov. 10, 1998 and 60/143,962, filed Jul. 15, 1999, and PCT International application no. PCT/EP99/07417, filed Sep. 24, 1999, the contents of each of which are hereby incorporated by reference.

The present invention concerns the use of pyrimidine derivatives having Human Immunodeficiency Virus (HIV) replication inhibiting properties. It also relates to a novel group of pyrimidine derivatives, their use as a medicine, their processes for preparation and pharmaceutical compositions comprising them.

EP-0,834,507 discloses substituted diamino 1,3,5-triazine derivatives having HIV replication inhibiting properties. The present compounds differ from the known 1,3,5-triazines by structure and by their improved HIV replication inhibiting properties.

The present invention is concerned with the use of compounds of formula (I):

(I)



the N-oxides, the pharmaceutically acceptable addition salts, the quaternary amines and the stereochemically isomeric forms thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula:

—CH=CH—CH=CH— (a-1);

—N=CH—CH=CH— (a-2);

—N=CH—N=CH— (a-3);

—N=CH—CH=N— (a-4);

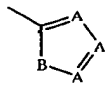
—N=N—CH=CH— (a-5);

n is 0, 1, 2, 3 or 4; and in case $-a^1=a^2-a^3=a^4-$ is (a-1), then n may also be 5;

R^1 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or —C(=O)R^6, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, —S(=O)$_p$$R^6$, —NH—S(=O)$_p$$R^6$, —C(=O)$R^6$, —NHC(=O)H, —C(=O)NHNH$_2$, —NHC(=O)$R^6$, —C(=NH)$R^6$ or a radical of formula:

(c)



wherein each A independently is N, CH or CR^6;

B is NH, O, S or NR^6;

p is 1 or 2; and

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

C_{3-7}cycloalkyl,

indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,

phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is —X—R^3 wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is —NR^1—, —NH—NH—, —N=N—, —O—, —C(=O)—, —CHOH—, —S—, —S(=O)— or —S(=O)$_2$—;

Q represents hydrogen, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl or —NR^{4}R^5; and

R^4 and R^5 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, —S(=O)$_p$$R^6$, —NH—S(=O)$_p$$R^6$, —C(=O)$R^6$, —NHC(=O)H, —C(=O)NHNH$_2$, —NHC(=O)$R^6$, —C(=NH)$R^6$, aryl and Het; or

R^4 and R^5 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}alkylidene;

Y represents hydroxy, halo, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or —C(=O)R^6, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, —S(=O)$_p$$R^6$, —NH—S(=O)

$_pR^6$, —C(=O)R^6, —NHC(=O)H, —C(=O)$NHNH_2$, —NHC(=O)R^6, —C(=NH)R^6 or aryl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhaloC_{1-6}alkyloxy;

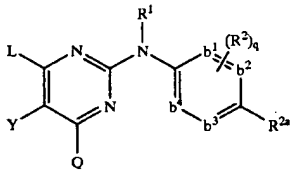
Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy;

for the manufacture of a medicine for the treatment of subjects suffering from HIV (Human Immunodeficiency Virus) infection.

The present invention also relates to a method of treating warm-blooded animals suffering from HIV (Human Immunodeficiency Virus) infection. Said method comprises the administration of a therapeutically effective amount of a compound of formula (I) or a N-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof in admixture with a pharmaceutical carrier.

This invention also relates to novel compounds having the formula:

(I-a)



the N-oxides, the addition salts, the quaternary amines and the stereochemically isomeric forms thereof, wherein

-b^1=b^2-C(R^{2a})=b^3-b^4= represents a bivalent radical of formula:

—CH=CH—C(R^{2a})=CH—CH= (b-1);

—N=CH—C(R^{2a})=CH—CH= (b-2);

—CH=N—C(R^{2a})=CH—CH= (b-3);

—N=CH—C(R^{2a})=N—CH= (b-4);

—N=CH—C(R^{2a})=CH—N= (b-5);

—CH=N—C(R^{2a})=N—CH= (b-6);

—N=N—C(R^{2a})=CH—CH= (b-7);

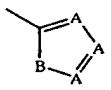
q is 0, 1, 2; or where possible q is 3 or 4;

R^1 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

R^{2a} is cyano, aminocarbonyl, mono- or di(methyl) aminocarbonyl, C_{1-6}alkyl substituted with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl, C_{2-6}alkenyl substituted with cyano, or C_{2-6}alkynyl substituted with cyano;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or —C(=O)R^6, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl) amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, —S(=O)$_pR^6$, —NH—S(=O)$_pR^6$, —C(=O)R^6, —NHC(=O)H, —C(=O)$NHNH_2$, —NHC(=O)R^6, —C(=NH)R^6 or a radical of formula:

(c)



wherein each A independently is N, CH or CR^6;

B is NH, O, S or NR^6;

p is 1 or 2; and

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

C_{3-7}cycloalkyl,

indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,

phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is —X—R^3 wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is —NR^1—, —NH—NH—, —N=N—, —O—, —C(=O)—, —CHOH—, —S—, —S(=O)— or —S(=O)$_2$—;

Q represents hydrogen, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl or —NR^4R^5; and

R^4 and R^5 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, —S(=O)$_pR^6$, —NH—S(=O)$_pR^6$, —C(=O)R^6, —NHC(=O)

H, —C(=O)NHNH$_2$, —NHC(=O)R^6, —C(=NH)R^6, aryl and Het; or

R^4 and R^5 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}alkylidene;

Y represents hydroxy, halo, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or —C(=O)R^6, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, —S(=O)$_p$R^6, —NH—S(=O)$_p$R^6, —C(=O)R^6, —NHC(=O)H, —C(=O)NHNH$_2$, —NHC(=O)R^6, —C(=NH)R^6 or aryl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhaloC_{1-6}alkyloxy;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

As used herein C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl, pentyl, hexyl, 2-methylpropyl, 2-methylbutyl and the like; C_{1-10}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 10 carbon atoms such as the groups defined for C_{1-6}alkyl and heptyl, octyl, nonyl, decyl and the like; C_{1-12}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 12 carbon atoms such as the groups defined for C_{1-10}alkyl and undecyl, dodecyl and the like; C_{1-4}alkylidene defines straight or branched chain saturated bivalent hydrocarbon radicals having from 1 to 4 carbon atoms such as methylene, 1,2-ethanediyl or 1,2-ethylidene, 1,3-propanediyl or 1,3-propylidene, 1,4-butanediyl or 1,4-butylidene and the like; C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{2-6}alkenyl defines straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms containing a double bond such as ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like; C_{2-10}alkenyl defines straight and branched chain hydrocarbon radicals having from 2 to 10 carbon atoms containing a double bond such as the groups defined for C_{2-6}alkenyl and heptenyl, octenyl, nonenyl, decenyl and the like; C_{2-6}alkynyl defines straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms containing a triple bond such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like; C_{2-10}alkynyl defines straight and branched chain hydrocarbon radicals having from 2 to 10 carbon atoms containing a triple bond such as the groups defined for C_{2-6}alkynyl and heptynyl, octynyl, nonynyl, decynyl and the like.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide group when attached once to a sulfur atom, and a sulfonyl group when attached twice to a sulfur atom.

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhalomethyl as a group or part of a group is defined as mono- or polyhalosubstituted methyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl; polyhaloC_{1-6}alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-6}alkyl, for example, the groups defined in halomethyl, 1,1-difluoroethyl and the like. In case more than one halogen atoms are attached to an alkyl group within the definition of polyhalomethyl or polyhaloC_{1-6}alkyl, they may be the same or different.

Het is meant to include all the possible isomeric forms of the heterocycles mentioned in the definition of Het, for instance, pyrrolyl also includes 2H-pyrrolyl.

The Het radical may be attached to the remainder of the molecule of formula (I) or (I-a) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heterocycle is pyridinyl, it may be 2-pyridinyl, 3-pyridinyl or 4-pyridinyl.

When any variable (eg. aryl, R^2, R^6 etc.) occurs more than one time in any constituent, each definition is independent.

Lines drawn into ring systems from substituents indicate that the bond may be attached to any of the suitable ring atoms.

It will be appreciated that some of the compounds of formula (I) or (I-a) and their N-oxides, addition salts, quaternary amines and stereochemically isomeric forms may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compounds of formula (I) or (I-a), and their N-oxides, addition salts, quaternary amines or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of formula (I) or (I-a) and their N-oxides, salts, solvates or quaternary amines substantially free, i.e. associated with less than 10%, preferably less than 5%, in particular less than 2% and most preferably less than 1% of the other isomers. In particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds of formula (I) or (I-a) are obviously intended to be embraced within the scope of this invention.

For therapeutic use, salts of the compounds of formula (I) or (I-a) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are not pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I) or (I-a) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for

example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I) or (I-a) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) or (I-a) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

Some of the compounds of formula (I) or (I-a) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

Whenever used hereinafter, the term "compounds of formula (I)" or "compounds of formula (I-a)" is meant to include also the N-oxides, the addition salts, the quaternary amines and all stereoisomeric forms.

A special group of compounds contains those compounds of formula (I) wherein R^1 is hydrogen, aryl, formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl.

Another special group of compounds contains those compounds of formula (I) wherein one or more of the following restrictions apply:

i) $-a^1=a^2-a^3=a^4-$ is a radical of formula (a-1);

ii) R^1 is hydrogen;

iii) n is 1;

iv) R^2 is cyano, preferably in the para position relative to the $—NR^1—$ group;

v) Y is cyano, $—C(=O)NH_2$ or a halogen, preferably a halogen;

vi) Q is hydrogen or $—NR^4R^5$ wherein R^4 and R^5 are preferably hydrogen;

vii) L is $—X—R^3$ wherein X is preferably NR^1, O or S, most preferably X is NH, and R^3 is substituted phenyl with C_{1-6}alkyl, halogen and cyano as preferred substituents.

Still another special group of compounds contains those compounds of formula (I-a) wherein R^1 is hydrogen, aryl, formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl.

Another special group of compounds contains also those compounds of formula (I-a) wherein one or more of the following restrictions apply:

i) $-b^1=b^2-C(R^{2a})=b^3-b^4=$ is a radical of formula (b-1);

ii) q is 0;

iii) R^{2a} is cyano or $—C(=O)NH_2$, preferably R^{2a} is cyano;

iv) Y is cyano, $—C(=O)NH_2$ or a halogen, preferably a halogen;

v) Q is hydrogen or $—NR^4R^5$ wherein R^4 and R^5 are preferably hydrogen;

vi) L is $—X—R^3$ wherein X is preferably NR^1, O or S, most preferably X is NH, and R^3 is substituted phenyl with C_{1-6}alkyl, halogen and cyano as preferred substituents.

An interesting group of compounds are those compounds of formula (I) or (I-a) wherein L is $—X—R^3$ wherein R^3 is 2,4,6-trisubstituted phenyl, each substituent independently selected from chloro, bromo, fluoro, cyano or C_{1-4}alkyl.

Also interesting are those compounds of formula (I) or (I-a) wherein Y is chloro or bromo and Q is hydrogen or amino.

Particular compounds are those compounds of formula (I) or (I-a) wherein the moiety in the 2 position of the pyrimidine ring is a 4-cyano-anilino group.

Preferred compounds are those compounds of formula (I) or (I-a) wherein the moiety in the 2 position of the pyrimidine ring is a 4-cyano-anilino group, L is $—X—R^3$ wherein R^3 is a 2,4,6-trisubstituted phenyl, Y is a halogen and Q is hydrogen or NH_2.

Most preferred compounds are:

4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

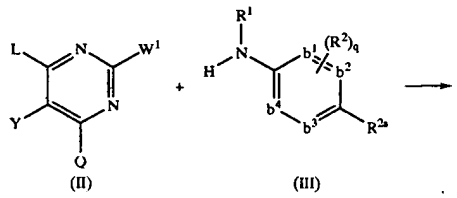
4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]benzonitrile; and

4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]benzonitrile; the N-oxides, the addition salts, the quaternary amines and the stereochemically isomeric forms thereof.

In general, compounds of formula (I-a) can be prepared by reacting an intermediate of formula (II) wherein W^1 is a suitable leaving group such as, for example, a halogen, hydroxy, triflate, tosylate, thiomethyl, methylsulfonyl, trifluoromethylsulfonyl and the like, with an amino derivative of formula (III) optionally under solvent-free conditions or in a reaction-inert solvent such as, for example, ethanol, 1-methyl-2-pyrrolidinone, N,N-dimethylformamide, 1,4-dioxane, tetrahydrofuran, dimethyl sulfoxide, tetraline, sulfolane, acetonitrile and the like, under a reaction-inert atmosphere such as, for example, oxygen free argon or nitrogen, and optionally in the presence of an acid such as, for example, 1 N hydrochloric acid in diethyl ether or the like. This reaction can be performed at a temperature ranging between 50° C. and 250° C.



(II) (III)

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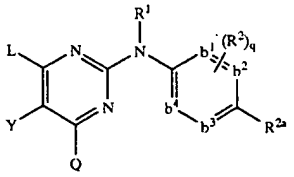
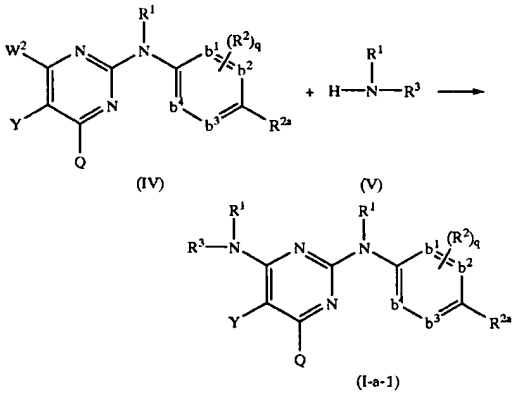


(I-a)

In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

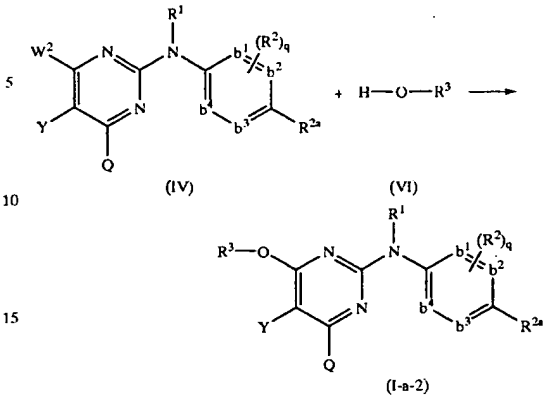
The compounds of formula (I-a) wherein L is a radical of formula —NR^1—R^3, said compounds being represented by formula (I-a-1), can be prepared by reacting an intermediate of formula (IV) wherein W^2 is a suitable leaving group such as, for example, a halogen or a triflate, with an intermediate of formula (V) under solvent-free conditions or in an appropriate solvent such as, for example, ethanol, 1-methyl-2-pyrrolidinone, N,N-dimethylformamide, 1,4-dioxane, tetrahydrofuran, dimethyl sulfoxide, tetraline, sulfolane, acetonitrile and the like, under a reaction-inert atmosphere such as, for example, oxygen free argon or nitrogen, and optionally in the presence of an acid such as, for example, 1 N hydrochloric acid in diethyl ether. This reaction can be performed at a temperature ranging between 50° C. and 250° C.



(IV) (V)

(I-a-1)

The compounds of formula (I-a) wherein L is a radical of formula —O—R^3, said compounds being represented by formula (I-a-2), can be prepared by reacting an intermediate of formula (IV) wherein W^2 is a suitable leaving group such as, for example a halogen or a triflate, with an intermediate of formula (VI) in an appropriate solvent such as, for example, 1,4-dioxane, dimethyl sulfoxide, tetraline, sulfolane and the like under a reaction-inert atmosphere such as, for example, oxygen free argon or nitrogen, and in the presence of a base such as, for example, sodium hydride, potassium hydride, sodium hydroxide or the like. This reaction can be performed at a temperature ranging between 50° C. and 250° C.



(IV) (VI)

(I-a-2)

The compounds of formula (I-a) may further be prepared by converting compounds of formula (I-a) into each other according to art-known group transformation reactions.

The compounds of formula (I-a) may be converted to the corresponding N-oxide forms following art-known procedures for converting a trivalent nitrogen into its N-oxide form. Said N-oxidation reaction may generally be carried out by reacting the starting material of formula (I-a) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

For instance, the compounds of formula (I-a) wherein Q is a halogen may be converted to the corresponding compounds wherein Q is —NR^4H using NH_2R^4 as a reagent in a reaction inert solvent such as, for example, 1,4-dioxane and the like, optionally in the presence of a suitable base such as, for example, triethylamine or N,N-diisopropylethylamine or the like. In case R^4 contains a hydroxy moiety, it may be convenient to perform the above reaction with a protected form of NH_2R^4 whereby the hydroxy moiety bears a suitable protecting group P being, for instance, a trialkylsilyl group, and subsequently removing the protective group according to art-known methodologies.

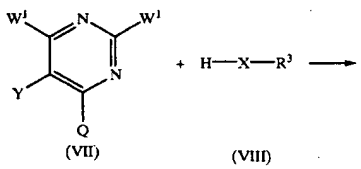
Some of the compounds of formula (I-a) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or

chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

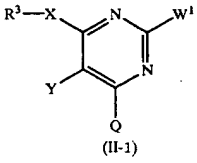
An alternative manner of separating the enantiomeric forms of the compounds of formula (I-a) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials are known compounds and may be commercially available or may be prepared according to art-known procedures.

Intermediates of formula (II) wherein L is —X—R^3, said intermediates being represented by formula (II-1) can be prepared by reacting a pyrimidine derivative of formula (VII) wherein each W^1 is as defined previously, with HXR^3 (VIII) in a reaction inert solvent such as, for example, 1,4-dioxane, 2-propanol or the like, and in the presence of a base such as, for example, triethylamine or N,N-diisopropylethylamine or the like. Different regio-specific isomers may be formed and can be separated from one another using suitable separation techniques such as, for example, chromatography.

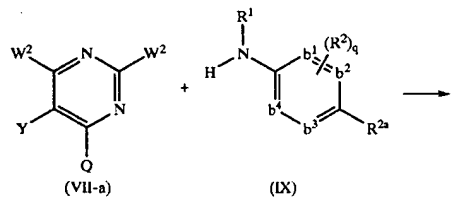


(VII) (VIII)



(II-1)

Intermediates of formula (IV) can be prepared by reacting an intermediate of formula (VII-a) wherein W^2 is a suitable leaving group such as, for example, a halogen, with an intermediate of formula (IX) in a suitable solvent such as, for example, 1-methyl-2-pyrrolidinone, 1,4-dioxane or the like, in the presence of an acid such as, for example, 1 N hydrochloric acid in diethyl ether. This reaction can be performed at a temperature ranging between 50° C. and 250° C.



(VII-a) (IX)

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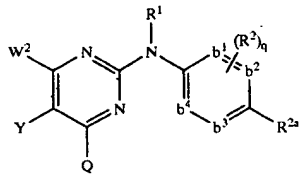
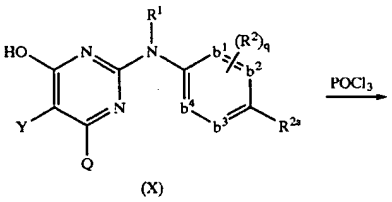
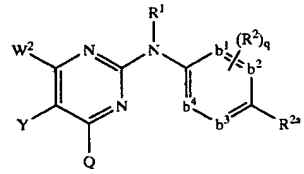


(IV)

Alternatively, intermediates of formula (IV) can be prepared by reacting an intermediate of formula (X) with phosphorous oxychloride, triflic anhydride or a functional derivative thereof under a reaction-inert atmosphere such as, for example, oxygen free argon or nitrogen. This reaction can be performed at a temperature ranging between 20° C. and 150° C.

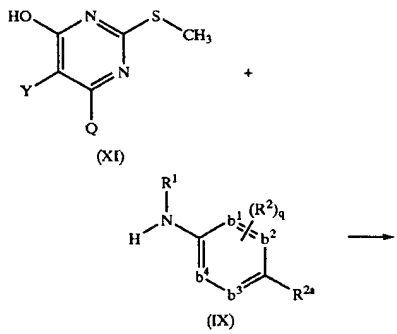


(X)



(IV)

Intermediates of formula (X) can be prepared by reacting an intermediate of formula (XI) or a functional derivative thereof, with an intermediate of formula (IX). This reaction may be performed under solvent-free conditions or in an appropriate solvent such as, for example, diglyme, tetraline or the like under a reaction-inert atmosphere such as, for example, oxygen free argon or nitrogen, and optionally in the presence of a base such as, for example, sodium hydride, potassium hydride or the like. This reaction can be performed at a temperature ranging between 100° C. and 250° C.



(XI) (IX)

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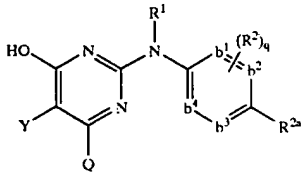
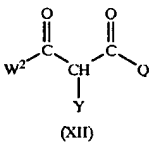
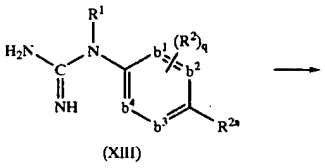


(X)

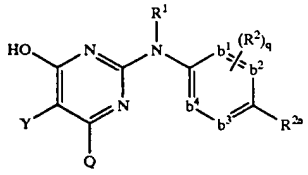
Intermediates of formula (X) can also be prepared by reacting an intermediate of formula (XII), wherein W^2 is a suitable leaving group and Y and Q are as defined for a compound of formula (I-a), with an intermediate of formula (XIII) in an appropriate solvent such as, for example, ethanol, or the like, and in the presence of a base such as, for example, sodium ethoxide or the like, under a reaction-inert atmosphere such as, for example, oxygen free argon or nitrogen. The reaction can be performed at a temperature ranging between 20° C. and 125° C.



(XII)

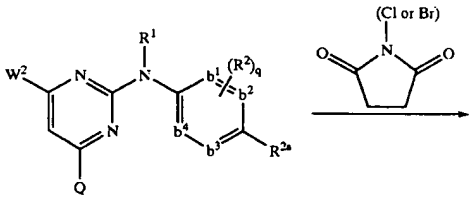


(XIII)



(X)

A convenient way of preparing an intermediate of formula (IV) wherein Y is a bromine or chloro atom, said intermediates being represented by formula (IV-1), involves the introduction of a bromine or chloro atom to an intermediate of formula (XIV), wherein W^2 is as previously defined, using N-bromosuccinimide or N-chlorosuccinimide in a reaction-inert solvent such as, for example, chloroform, carbon tetrachloride or the like. This reaction can be performed at a temperature ranging between 20° C. and 125° C.



(XIV)

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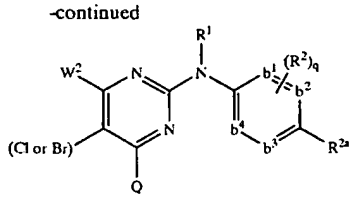


(IV-1)

Analogous to the conversion of compounds of formula (I-a) wherein Q is a halogen to compounds of formula (I-a) wherein Q is —NHR^4, the intermediates of formula (II), (IV) and (VII) can also be converted.

The compounds of formula (I-a) as prepared in the hereinabove described processes may be synthesized as a mixture of stereoisomeric forms, in particular in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I-a) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I-a) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

It will be appreciated by those skilled in the art that in the processes described above the functional groups of intermediate compounds may need to be blocked by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl groups (e.g. tert-butyldimethylsilyl, tert-butyldiphenylsilyl or trimethylsilyl), benzyl and tetrahydropyranyl. Suitable protecting groups for amino include tert-butyloxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C_{1-6}alkyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after a reaction step.

The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis' 2nd edition, T W Greene & P G M Wutz, Wiley Interscience (1991).

The compounds of formula (I) and (I-a) show antiretroviral properties, in particular against Human Immunodeficiency Virus (HIV), which is the aetiological agent of Acquired Immune Deficiency Syndrome (AIDS) in humans. The HIV virus preferentially infects human T-4 cells and destroys them or changes their normal function, particularly the coordination of the immune system. As a result, an infected patient has an everdecreasing number of T-4 cells, which moreover behave abnormally. Hence, the immunological defense system is unable to combat infections and neoplasms and the HIV infected subject usually dies by opportunistic infections such as pneumonia, or by cancers.

Other conditions associated with HIV infection include thrombocytopaenia, Kaposi's sarcoma and infection of the central nervous system characterized by progressive demyelination, resulting in dementia and symptoms such as, progressive dysarthria, ataxia and disorientation. HIV infection further has also been associated with peripheral neuropathy, progressive generalized lymphadenopathy (PGL) and AIDS-related complex (ARC).

The present compounds also show activity against HIV-1 strains that have acquired resistance to art-known non-nucleoside reverse transcriptase inhibitors. They also have little or no binding affinity to human α-1 acid glycoprotein.

Due to their antiretroviral properties, particularly their anti-HIV properties, especially their anti-HIV-1-activity, the compounds of formula (I) or (I-a), their N-oxides, pharmaceutically acceptable addition salts, quaternary amines and stereochemically isomeric forms thereof, are useful in the treatment of individuals infected by HIV and for the prophylaxis of these infections. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses whose existence is mediated by, or depends upon, the enzyme reverse transcriptase. Conditions which may be prevented or treated with the compounds of the present invention, especially conditions associated with HIV and other pathogenic retroviruses, include AIDS, AIDS-related complex (ARC), progressive generalized lymphadenopathy (PGL), as well as chronic CNS diseases caused by retroviruses, such as, for example HIV mediated dementia and multiple sclerosis.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines against above-mentioned conditions. Said use as a medicine or method of treatment comprises the systemic administration to HIV-infected subjects of an amount effective to combat the conditions associated with HIV and other pathogenic retroviruses, especially HIV-1.

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

To aid solubility of the compounds of formula (I-a), suitable ingredients, e.g. cyclodextrins, may be included in the compositions. Appropriate cyclodextrins are α-, β-, γ-cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6}alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD; hydroxyC_{1-6}alkyl, particularly hydroxyethyl, hydroxy-propyl or hydroxybutyl; carboxyC_{1-6}alkyl, particularly carboxymethyl or carboxy-ethyl; C_{1-6}alkylcarbonyl, particularly acetyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy) propyl-β-CD, and in particular 2-hydroxypropyl-β-CD (2-HP-β-CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The M.S. and D.S. value can be determined by various analytical techniques such as nuclear magnetic resonance (NMR), mass spectrometry (MS) and infrared spectroscopy (IR). Depending on the technique used, slightly different values may be obtained for one given cyclodextrin derivative. Preferably, as measured by mass spectrometry, the M.S. ranges from 0.125 to 10 and the D.S. ranges from 0.125 to 3.

Other suitable compositions for oral or rectal administration comprise particles obtainable by melt-extruding a mixture comprising a compound of formula (I-a) and an appropriate water-soluble polymer and subsequently milling said melt-extruded mixture. Said particles can then be formulated by conventional techniques into pharmaceutical dosage forms such as tablets and capsules.

Said particles consist of a solid dispersion comprising a compound of formula (I-a) and one or more pharmaceutically acceptable water-soluble polymers. The preferred technique for preparing solid dispersions is the melt-extrusion process comprising the following steps:

a) mixing a compound of formula (I-a) and an appropriate water-soluble polymer,

b) optionally blending additives with the thus obtained mixture,

c) heating the thus obtained blend until one obtains a homogenous melt,

d) forcing the thus obtained melt through one or more nozzles; and

e) cooling the melt till it solidifies.

The solid dispersion product is milled or ground to particles having a particle size of less than 1500 μm, preferably less than 400 μm, more preferably less than 250 μm and most preferably less than 125 μm.

The water-soluble polymers in the particles are polymers that have an apparent viscosity, when dissolved at 20° C. in an aqueous solution at 2% (w/v), of 1 to 5000 mPa·s, more preferably of 1 to 700 mPa·s, and most preferred of 1 to 100 mPa·s. For example, suitable water-soluble polymers include alkylcelluloses, hydroxyalkyl-celluloses, hydroxyalkyl alkylcelluloses, carboxyalkylcelluloses, alkali metal salts of carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters, starches, pectines, chitin derivates, polysaccharides, polyacrylic acids and the salts thereof, polymethacrylic acids and the salts and esters thereof, methacrylate copolymers, polyvinylalcohol, polyalkylene oxides and copolymers of ethylene oxide and propylene oxide. Preferred water-soluble polymers are Eudragit E® (Röhm GmbH, Germany) and hydroxypropyl methylcelluloses.

Also one or more cyclodextrins can be used as water soluble polymer in the preparation of the above-mentioned particles as is disclosed in WO 97/18839. Said cyclodextrins include the pharmaceutically acceptable unsubstituted and substituted cyclodextrins known in the art, more particularly α, β or γ cyclodextrins or the pharmaceutically acceptable derivatives thereof.

Substituted cyclodextrins which can be used include polyethers described in U.S. Pat. No. 3,459,731. Further substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-6}alkyl, hydroxyC_{1-6}alkyl, carboxy-C_{1-6}alkyl or C_{1-6}alkyloxycarbonylC_{1-6}alkyl or mixed ethers thereof. In particular such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-3}alkyl, hydroxyC_{2-4}alkyl or carboxyC_{1-2}alkyl or more in particular by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxy-methyl or carboxyethyl.

Of particular utility are the β-cyclodextrin ethers, e.g. dimethyl-β-cyclodextrin as described in Drugs of the Future, Vol. 9, No. 8, p. 577–578 by M. Nogradi (1984) and polyethers, e.g. hydroxypropyl β-cyclodextrin and hydroxyethyl β-cyclodextrin, being examples. Such an alkyl ether may be a methyl ether with a degree of substitution of about 0.125 to 3, e.g. about 0.3 to 2. Such a hydroxypropyl cyclodextrin may for example be formed from the reaction between β-cyclodextrin an propylene oxide and may have a MS value of about 0.125 to 10, e.g. about 0.3 to 3.

A more novel type of substituted cyclodextrins is sulfobutylcyclodextrines.

The ratio of the compound of formula (I-a) over cyclodextrin may vary widely. For example ratios of 1/100 to 100/1 may be applied. Interesting ratios of the compound of formula (I-a) over cyclodextrin range from about 1/10 to 10/1. More interesting ratios range from about 1/5 to 5/1.

It may further be convenient to formulate the compounds of formula (I-a) in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Useful surface modifiers are believed to include those which physically adhere to the surface of the compound of formula (I-a) but do not chemically bond to said compound.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.

Yet another interesting way of formulating the compounds of formula (I-a) involves a pharmaceutical composition whereby the compounds of formula (I-a) are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration.

Said beads comprise a central, rounded or spherical core, a coating film of a hydrophilic polymer and a compound of formula (I-a) and a seal-coating polymer layer.

Materials suitable for use as cores in the beads are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

Those of skill in the treatment of HIV-infection could determine the effective daily amount from the test results presented here. In general it is contemplated that an effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, more preferably from 0.1 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) or (I-a) used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines and are not intended to limit the scope or use of the invention to any extent.

Also, the combination of an antiretroviral compound and a compound of formula (I) or (I-a) can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I) or (I-a), and (b) another antiretroviral compound, as a combined preparation for simultaneous, separate or sequential use in anti-HIV treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. Said other antiretroviral compounds may be known antiretroviral compounds such as nucleoside reverse

transcriptase inhibitors, e.g. zidovudine (3'-azido-3'-deoxythymidine, AZT), didanosine (dideoxy inosine; ddI), zalcitabine (dideoxycytidine, ddC) or lamivudine (3'-thia-2'-3'-dideoxycytidine, 3TC) and the like; non-nucleoside reverse transciptase inhibitors such as suramine, pentamidine, thymopentin, castanospermine, efavirenz, dextran (dextran sulfate), foscarnet-sodium (trisodium phosphono formate), nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b: 2', 3'-e][1,4]diazepin-6-one), tacrine (tetrahydroaminoacridine) and the like; compounds of the TIBO (tetrahydro-imidazo[4,5,1-jk][1,4]-benzodiazepine-2(1H)-one and thione)-type e.g. (S)-8-chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl) imidazo-[4,5,1-jk][1,4]benzodiazepine-2(1H)-thione; compounds of the α-APA (α-anilino phenyl acetamide) type e.g. α-[(2-nitro-phenyl)amino]-2,6-dichlorobenzene-acetamide and the like; TAT-inhibitors, e.g. RO-5-3335 and the like; protease inhibitors e.g. indinavir, ritanovir, saquinovir, ABT-378 and the like; or immunomodulating agents, e.g. levamisole and the like. The compound of formula (I) or (I-a) can also be combined with another compound of formula (I) or (I-a).

The following examples are intended to illustrate the present invention.

EXPERIMENTAL PART

A. Preparation of the Intermediate Compounds

EXAMPLE A1

Reaction under argon atmosphere. A solution of 2,4,6-trimethylbenzenamine (0.00461 mol) in 1,4-dioxane (5 ml) was added to a solution of 5-bromo-2,4-dichloropyrimidine (0.00439 mol) in 1,4-dioxane (5 ml). N,N-bis(1-methylethyl)ethanamine (0.00548 mol) was added. The reaction mixture was stirred and refluxed for 20 hours. The solvent was evaporated. The residue was dissolved in ethyl acetate, washed with a saturated aqueous sodium bicarbonate solution, water and brine, dried with sodium sulfate, filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: 1:5, 1:2 and 1:1 CH_2Cl_2: hexane). Two pure fraction groups were collected and their solvent was evaporated, yielding 0.35 g (24%) of 5-bromo-4-chloro-N-(2,4,6-trimethylphenyl)-2-pyrimidinamine (interm. 1) and 0.93 g (65%) of 5-bromo-2-chloro-N-(2,4,6-trimethylphenyl)-4-pyrimidinamine (interm. 2).

EXAMPLE A2

a) 4-Hydroxy-5-chloro-2-methylthiopyrimidine (0.0156 mol) and 4-aminobenzonitrile (0.078-mol) were combined as a melt and stirred at 180–200° C. for 6 hours. The reaction mixture was cooled, and triturated sequentially with boiling CH_2Cl_2 and CH_3CN to obtain 95% pure compound, which was dried, yielding 1.27 g (33%) of 4-[(5-chloro-4-hydroxy-2-pyrimidinyl)amino]benzonitrile (interm. 3; mp. >300° C.).

b) $POCl_3$ (10 ml) was added to intermediate (3) (0.0028 mol). The flask was equipped with a condenser and heated to 80° C. for 35 minutes. The material was quenched on ice and allowed and the resulting precipitate was collected and washed with water (50 ml). The sample was dried. A fraction thereof was further purified by column chromato-graphy. The pure fractions were collected and the solvent was evaporated, yielding 4-[(4,5-dichloro-2-pyrimidinyl)amino] benzonitrile (interm. 4).

c) The mixture of intermediate (4) (0.0132 mol) in tetrahydrofuran (75 ml) and CH_2Cl_2 (10 ml) was stirred for 15 min. HCl in diethyl ether (0.0145 mol) was added slowly, and the mixture was stirred for 5 minutes. The solvent was removed under reduced pressure, yielding 3.98 g of 4-[(4,5-dichloro-2-pyrimidinyl)amino]benzonitrile monohydrochloride (interm. 5).

EXAMPLE A3

a)2,4,5,6-tetrachloropyrimidine (0.0134 mol), 1,4-dioxane (30 ml), 2,4,6-trimethyl aniline (0.0134 mol), and N,N-bis(1-methylethyl)ethanamine (0.0136 mol) were added to a flask under argon and stirred at 55° C. for 16 hours. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, then purified by column chromatography over silica gel (eluent: CH_2Cl_2/hexane 1/4, and 1/2). The desired fractions were collected and their solvent was evaporated, yielding 0.15 g 4,5,6-trichloro-N-(2,4,6-trimethylphenyl)-2-pyrimidinamine (interm. 6) and 3.15 g 2,5,6-trichloro-N-(2,4,6-trimethylphenyl)-4-pyrimidinamine (interm. 7).

b) A mixture of intermediate 7 (0.00474 mol) in NH_3, (2.0 M in 2-propanol; 20 ml) was heated in a pressure vessel at 75–80° C. for 40 hours. The temperature was increased to 110–115° C. The solvent was evaporated to produce 1.85 g of residue. The sample was heated with NH_3, (0.5 M in 1,4-dioxane; 20 ml) at 125° C. for 18 hours. The solvent was evaporated, yielding 1.7 g of a mixture of two isomers, i.e. 2,5-dichloro-N4-(2,4,6-trimethylphenyl)-4,6-pyrimidinediamine (interm. 8) and 5,6-dichloro-N4-(2,4,6-trimethylphenyl)-2,4-pyrimidinediamine (interm. 9).

EXAMPLE A4

a) A mixture of 4-[(1,4-dihydro-4-oxo-2-pyrimidinyl) amino]benzonitrile, (0.12 mol) in $POCl_3$ (90 ml) was stirred and refluxed under Argon for 20 minutes. The reaction mixture was slowly poured onto 750 ml ice/water, and the solid was separated by filtration. The solid was suspended in 500 ml water, and the pH of the suspension was adjusted to neutral by adding a 20% NaOH solution. The solid was again separated by filtration, suspended in 200 ml 2-propanone, and 1000 ml CH_2Cl_2 was added. The mixture was heated until all solid had dissolved. After cooling to room temperature, the aqueous layer was separated, and the organic layer was dried. During removal of the drying agent by filtration, a white solid formed in the filtrate. Further cooling of the filtrate in the freezer, followed by filtration, yielded 21.38 g (77.2%) of 4-[(4-chloro-2-pyrimidinyl) amino]benzonitrile (interm. 10).

b) Intermediate (10) (0.005 mol), 1-bromo-2,5-pyrrolidinedione (0.006 mol) and trichloromethane (10 ml) were combined in a sealed tube and heated at 100° C. overnight. The reaction mixture was allowed to cool to room temperature. Silica gel (2 g) was added, and the solvent was evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/hexanes 9/1). The pure fractions were collected and the solvent was evaporated, yielding 1.31 g (84.5%) of 4-[(5-bromo-4-chloro-2-pyrimidinyl)amino]benzonitrile (interm. 11).

EXAMPLE A5

To a flask under Argon was added 4-amino-2,5,6-trichloropyrimidine (0.08564 mol), 4-amino-benzonitrile (0.1071 mol), 1-methyl-2-pyrrolidinone (17 ml) and HCl in diethylether (1M; 85.6 ml). The mixture was placed in an oil bath at 130° C. under a stream of nitrogen until the ether was gone. An additional 10 ml of 1-methyl-2-pyrrolidinone was added. The mixture was heated at 145° C. for 16 hours under

argon. 1,4-Dioxane was added. The mixture was refluxed, cooled, then filtered. The filtrate was evaporated. The residue was dissolved in CH_2Cl_2, washed with 1 N NaOH, then filtered. The solid was dissolved in 2-propanone, evaporated onto silica gel, and chromatographed using 1–3% 2-propanone in hexane as eluent. The pure fractions were collected and the solvent was evaporated, yielding 1.63 g (6.8%) of 4-[(4-amino-5,6-dichloro-2-pyrimidinyl)amino] benzonitrile (interm. 12).

B. Preparation of the Final Compounds

EXAMPLE B1

a) To a flask under argon containing intermediate (1) (0.00107 mol) was added ether. To this homogeneous solution was added HCl/diethylether (1M; 0.00109 mol). The solvent was evaporated and 1,4-dioxane (35 ml) and 4-aminobenzonitrile (0.00322 mol) were added. The reaction mixture was stirred and refluxed for 4 days. The solvent was evaporated. The residue was dissolved in CH_2Cl_2, washed with a saturated sodium bicarbonate solution, dried, filtered and the solvent was evaporated to give 0.79 g of amber oil. The oil was purified by reverse phase HPLC. The desired fractions were collected and the solvent was evaporated, yielding residues 1 and 2.

Residue 1 was purified by column chromatography over silica gel (eluent: 0 and 2% CH_3OH:CH_2Cl_2). The pure fractions were collected and the solvent was evaporated, yielding 0.0079 g (2.0%) of 4-[[5-chloro-2-[(2,4,6-trimethylphenyl)amino]-4-pyrimidinyl]amino]benzonitrile (compound 1).

Residue 2 was purified by column chromatography over silica gel (eluent: 0 and 2% CH_3OH:CH_2Cl_2). The pure fractions were collected and the solvent was evaporated, yielding 0.0044 g (1.0%) of 4-[[5-bromo-2-[(2,4,6-trimethylphenyl)amino]-4-pyrimidinyl]amino]benzonitrile (compound 2).

b) To a flask containing intermediate 2 (0.00285 mol) was added ether. To this homogeneous solution was added HCl in diethyl ether (1M; 0.00855 mol). The solvent was evaporated and 1,4-dioxane (20 ml) was added. Finally, 4-aminobenzonitrile (0.00291 mol) and 1,4-dioxane (15 ml) were added and the reaction mixture was stirred and refluxed for seven days. The solvent was evaporated, the residue dissolved in CH_2Cl_2, washed with 1 M NaOH, and the solvent evaporated. The residue was dissolved in CH_2Cl_2 (10 ml) and the precipitate was filtered off and dried, yielding 0.15 g (13%) of 4-[[5-bromo-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (comp. 3).

EXAMPLE B2

a) A 3:1 mixture of intermediate (8) and intermediate (9) [as prepared in example A3b] and 4-aminobenzonitrile (0.01422 mol) was heated in a pressure vessel at 180° C. for 5 hours. The sample was partitioned between CH_2Cl_2 and diluted $NaHCO_3$, dried over K_2CO_3, filtered, and evaporated. CH_3CN was stirred in, the resulting precipitate removed by filtration. The filtrate was further purified by reverse phase HPLC. The pure fractions were collected and the solvent was evaporated, yielding 0.17 g of 4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl] amino]benzonitrile trifluoroacetate (1:1) (comp. 4).

EXAMPLE B3

HCl in diethylether (1M; 0.0045 mol) was added to a suspension of intermediate (4) (0.003 mol) in 1,4-dioxane (5 ml), stirred under argon in a sealable tube. The mixture was warmed to evaporate the diethylether, and 2,4,6-trimethylbenzenamine (0.009 mol) was added. The tube was sealed, and the reaction mixture was heated to 150° C. for 12 hours. The reaction mixture was allowed to cool to room temperature. Sequentially, silica gel (2.2 g) and CH_3OH (50 ml) were added. After evaporating the solvent, the residue was purified by flash chromatography (eluent gradient: CH_2Cl_2:CH_3OH: NH4OH 99.5:0.45:0.05 up to 99:0.9:0.1). The pure fractions were collected and the solvent was evaporated. The residue was dried, yielding 0.80 g (73.4%) of 4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (comp. 5).

EXAMPLE B4

A mixture of intermediate (5) (0.0025 mol) and 2,6-dibromo-4-methylbenzenamine (0.0075 mol) in 1,3-dioxane (5.0 ml) in a sealed tube under argon was heated and stirred at 160° C. for 16 hours. The reaction mixture was concentrated by rotary evaporation onto silica gel (2.0 g). The material was purified by flash chromatography (eluent 1:1 hexanes: CH_2Cl_2; neat CH_2Cl_2; 0.5%, 1% (10% NH_4OH in CH_3OH) in CH_2Cl_2) for 90% purity. Recrystallization afforded 0.15 g (12.2%) of 4-[[5-chloro-4-[(2,6-dibromo-4-methylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (comp. 10; 95% purity).

EXAMPLE B5

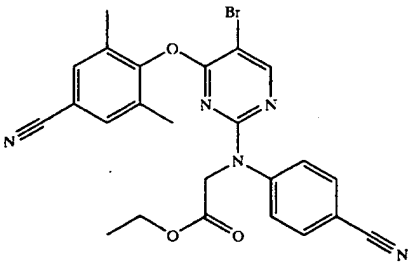
NaH (0.0075 mol; 60% suspension in oil) was added to a suspension of 2,4,6-trimethyl-phenol (0.0075 mol) in 1,4-dioxane (5 ml) in a sealable tube under argon. The mixture was stirred for 15 minutes, and intermediate (4) (0.0025 mol) was added. The tube was sealed, and the reaction mixture was heated to 150° C. for 15 hours. The reaction was allowed to cool to room temperature. After silica gel (2.0 g) was added, the solvent was evaporated. The residue was purified by flash column chromatography over silica gel (eluent gradient: CH_2Cl_2: hexanes 9:1 up to 100:0; then CH_2Cl_2:CH_3OH:NH_4OH 100:0:0 up to 97:2.7:0.3). The pure fractions were collected and the solvent was evaporated. The residue was dried, yielding 0.73 g of (80.2%) 4-[[5-chloro-4-(2,4,6-trimethylphenoxy)-2-pyrimidinyl] amino]benzonitrile (comp. 6).

EXAMPLE B6

a) NaH, 60% suspension in oil (0.003 mol) and 1-methyl-2-pyrrolidinone (3 ml) were added to a suspension of 4-hydroxy-3,5-dimethylbenzonitrile (0.003 mol) in 1,4-dioxane (3 ml) in a sealable tube under argon. After the H_2 had evolved, intermediate (11) (0.001 mol) was added. The tube was sealed and the reaction mixture was heated to 160° C. for 16 hours. The mixture was cooled to room temperature, transferred to a beaker and diluted with methanol (20 ml). Water (200 ml) was added dropwise. The aqueous mixture was extracted with CH_2Cl_2/CH_3OH 90/10 (3x300 ml). The organic layer was separated, dried, filtered and adsorbed onto silica gel (1 g). The solvent was evaporated and the residue was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/NH_4OH from 100/0/0 to 98/1.8/0.2). The desired fractions were collected and the solvent was evaporated. The residue was triturated with hot CH_3CN, filtered off, then dried, yielding 0.20 g (47.6%) of 4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile (comp. 17).

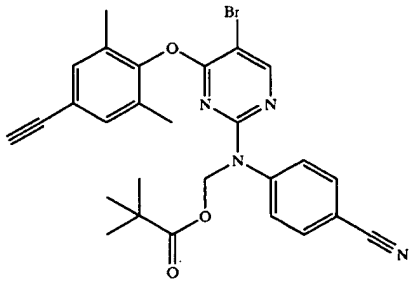
b) n-Butyllithium (0.010 mol) was added to a solution of N-(1-methylethyl)-2-propanamine (0.010 mol) in tetrahy-

drofuran (250 ml), stirred at 0° C. After stirring cold for 30 min, compound (17) (0.005 mol) was added. The resulting mixture was stirred cold for 15 min at which point ethyl 2-bromoethanoate (0.015 mol) was added and the temperature was allowed to rise to room temperature and the reaction mixture was stirred for 16 hours which drove the reaction to 50% completion. Quenched with 0.5 ml H_2O, the sample was concentrated by rotary evaporation onto silica gel, and purified by flash chromatography (Biotage Flash 40M, eluting with 0, 0.5, 1% (10% NH_4OH in CH_3OH) in CH_2Cl_2) to give a white solid which was 1:1 starting material A:product. Preparatory HPLC purification eluting into tubes containing 1 mmol $NaHCO_3$ effected final purification. Lyophilized material was taken up in water/CH_2Cl_2 (1:1 (50 ml total)) and separated. The aqueous phase was extracted 2 more times with 25 ml CH_2Cl_2. The organic layers were combined and dried over sodium sulfate, filtered and rotary evaporated to white solid dried in vacuo at 65° C. 18 hours. Yield: 0.33 g of



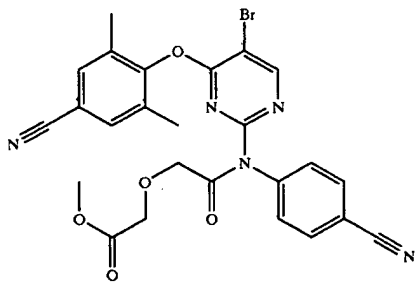
(13%, white solid); mp. 185–190° C. (comp. 59).

c) Reaction under Ar flow. NaH 60% (0.00600 mol) was stirred in tetrahydrofuran (20 ml). Compound (17) (0.00476 mol) was added and the mixture was stirred for 15 min. Chloromethyl-2,2-dimethylpropanoate (0.00600 mol) was added and the reaction mixture was stirred for 16 hours at room temperature, then stirred and refluxed for 4.5 hours, then cooled. Tetrahydrofuran (20 ml) was added. NaH 60% (0.00600 mol) and chloromethyl-2,2-dimethylpropanoate (0.00600 mol) were added and the resulting reaction mixture was stirred for 24 hours. The solvent was evaporated. The residue was dissolved in CH_2Cl_2, washed with water, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0 and 99.5/0.5). The desired fractions were collected and the solvent was evaporated. The residue was purified on the Gilson. This fraction was crystallized from 2-propanol, filtered off and dried. Yield: 0.60 g of



(23.6%, white solid) (comp. 60).

d) A suspension of compound (17) (0.0020 mol) in tetrahydrofuran (40 ml) was treated with 0.24 g of NaH in one portion. The effervescent mixture was stirred for 2 hours to afford a bright yellow suspension. A solution of 2,2'-oxybisacetyl chloride (0.020 mol) in tetrahydrofuran (10 ml) was prepared and cooled in an ice bath. Via cannula, the resultant A/B suspension was transferred to the cold solution of 2,2'-oxybisacetyl chloride dropwise over 10 minutes. The mixture was warmed to room temperature and stirred for 3 days. Another 0.24 g of NaH was added and after 2 days the reaction was cooled in an ice bath and treated with a mixture of methanol (0.150 mol) and N,N-diethylethanamine (0.150 mol) dropwise over 30 minutes. The reaction mixture was warmed to room temperature and after 16 hours poured into ether and extracted with saturated $NaHCO_3$. The aqueous fraction was extracted 2x with ether and the combined ether extracts were backwashed 3x with water and dried over $MgSO_4$. Concentration afforded 2.91 g of an oily residue that was subjected to reverse phase prep HPLC. Lyophilization of the appropriate fractions provided 0.16 g of the



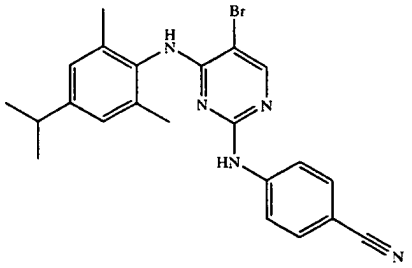
sample as a beige powder (14.5% purified yield) (comp. 61).

EXAMPLE B7

To a pressure vessel under argon was added intermediate 12 (0.00286 mol), 4-cyano-2,6-dimethylaniline (0.00571 mol), 1M HCl in diethyl ether (0.00140 mol) and 1,4-dioxane (8 ml). The reaction mixture was heated in an oil bath under a stream of nitrogen until all the solvents had evaporated. 1-methyl-2-pyrrolidinone (3 ml) was added, and the reaction mixture heated at 220–240° C. for 3 hours. Heating was continued at 210–220° C. for 6 hours. The residue was dissolved in 1,4-dioxane, evaporated, partitioned between CH_2Cl_2 and 1 N NaOH, filtered, dried organic layers with potassium carbonate and evaporated. The desired compound was isolated and purified by preparative reverse phase chromatography. The pure fractions were collected and the solvent was evaporated, yielding 0.0165 g (1.1% after lyophilization) of 4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile trifluoroacetate (1:1) (comp. 19).

EXAMPLE B8

A mixture of intermediate (11) (0.0011 mol), 2,6-dimethyl-4-(2-propyl)benzenamine (0.0011 mol), N,N,N',N'-tetramethyl-1,8-naphthalenediamine (0.0022 mol) and 1 M HCl in ether (2.3 ml) (0.0023 mol) in 1,4-dioxane (25 ml) was stirred and heated to 95° C. for 16 hours. Solvent was removed by rotary evaporation and the residue was purified by reverse phase preparatory HPLC. The combined fractions containing the desired material were lyophilized to yield 0.23 g of



(48%); mp. 198–201° C. (comp. 40)

EXAMPLE B9

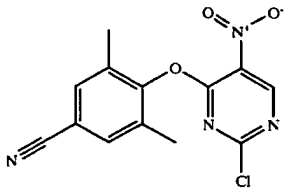
N,N-di(methylethyl)ethanamine (0.0024 mol) was added to 4-amino-2,5-dimethyl-3,4-benzonitrile (0.00219 mol) and 4-[[(5-bromo-4,6-dichloro)-2-pyrimidinyl]amino]-benzonitrile (0.00218 mol). The reaction vial was sealed and heated to 155–160° C. with stirring for 1.5 days. The sample was cooled to room temperature. The sample was treated with flash column chromatography over silica gel (eluent: CH_2Cl_2). Purification was completed through preparative HPLC to yield 0.05 g of 4-[[5-bromo-4-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino] benzonitrile (5.0%); mp. 259–260° C. (comp. 42).

EXAMPLE B10

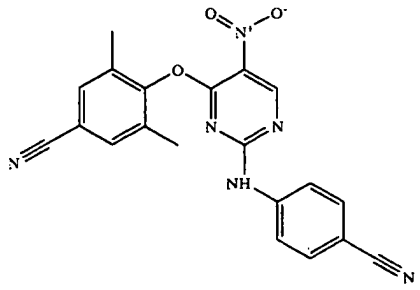
Sequentially 2,4,6-trimethylbenzenamine (0.0022 mol) and N,N-di(methylethyl)-ethanamine (0.0024 mol) were added to a solution of and 4-[[(5-bromo-4,6-dichloro)-2-pyrimidinyl]amino]benzonitrile (0.00218 mol) in 1,4-dioxane (10 ml). The tube was sealed and the suspension was heated to 120–130° C. in an oil bath while stirring for 90 hours. The mixture was cooled to room temperature. More N,N-di(methylethyl)-ethanamine (15 ml) was added, and the sample was reheated to 120–130° C. for 64 hours. The reaction was heated at 150° C. for 6 days. The sample was cooled to room temperature. The sample was diluted with ethylacetate and extracted with cold 1M NaOH. The aqueous phase was backwashed with ethylacetate. The combined organic phases were dried and concentrated. Flash column chromatography over silica gel (eluent: CH_2Cl_2). The sample was further purified by preparatory HPLC to yield 0.53 g of 4-[[5-bromo-4-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]-benzonitrile (54.9%); mp. 220–221° C. (comp. 41).

EXAMPLE B11

A mixture of 4-aminobenzonitrile (0.0043 mol) and



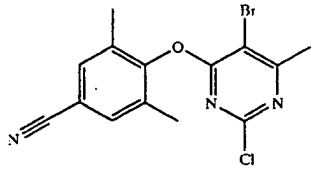
(0.0021 mol) in 1,4-dioxane (30 ml) was stirred at 100° C. for 16 hours. The solvent was removed by rotary evaporation. The solid residue was triturated and the residue was dried in vacuo at 40° C. for 16 hours, yielding 0.452 g of



(55%); mp. >300° C. (comp. 43).

EXAMPLE B12

To a pressure vessel was added



(0.00567 mol),

4-aminobenzonitrile (0.01163 mol) and 1-methyl-2-pyrrolidinone (20 ml). The reaction mixture was heated at 140° C. for 16 hours. The reaction mixture was cooled to room temperature and acetonitrile and water were added. The resulting precipitate was filtered, and the solid recrystallized with acetonitrile to give 1.27 g of 4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-6-methyl-2-pyrimidinyl] amino]benzonitrile (52); mp. 260–262° C. (comp. 44).

EXAMPLE B13

Intermediate (11) (0.001 mol) and 2,6-dimethyl-4-aminobenzonitrile (0.00473 mol) were combined and heated to 150° C. while stirring for 16 hours. The sample was dissolved in CH_3OH and evaporated onto silica gel (1 g) and eluted with 1:1 hexanes: CH_2Cl_2, 4:1 CH_2Cl_2:hexanes, and neat CH_2Cl_2 (2 L). The desired fractions were evaporated and the residue was dried in vacuo for 16 hours at 45° C. The thus obtained was transferred to a 4 ml vial in CH_2Cl_2 and the solvent was evaporated, yielding 0.120 g of 4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile (28.6%); mp. 277–280° C. (comp. 45).

EXAMPLE B14

4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-6-chloro-2-pyrimidinyl]amino]-benzonitrile (0.00250 mol) and NH_3/1,4-dioxane 0.5M (0.015 mol) were heated in a pressure vessel at 150° C. for 4 days. The sample was allowed to sit at ambient conditions for 2 days. Water was added slowly to the mixture until a precipitate formed. The mixture was stirred for 2 hours and filtered. The solid was recrystallized from CH_3CN to obtain 0.58 g (fraction 1). The filtrate was evaporated (fraction 2). Both fractions were combined and purified by column chromatography, eluting with CH_2Cl_2. The resulting residue of the desired fraction was recrystallized from CH_3CN to yield 0.44 g of 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]-amino]

benzonitrile (40.5%). The sample was dried at 80° C. for 16 hours at 0.2 mm Hg (comp. 46).

EXAMPLE B15

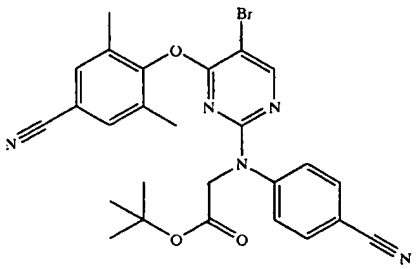
4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-6-chloro-2-pyrimidinyl]amino]-benzonitrile (0.000660 mol), tetrahydrofuran (1 ml), and 1-pyrrolidineethanamine (0.00198 mol) were added to a pressure vessel. The mixture was heated at 75° C. for 16 hours. CH_2Cl_2 was added, and the mixture was washed with water, dried, filtered and the filtrate was evaporated. Purification using flash column chromatography eluting with 1:9 methanol:methylene chloride produced a solid which was redissolved in CH_3CN. HCl/diethylether 1.0M (0.48 ml) was added, and the mixture was cooled in ice. Filtration yielded 0.19 g of 4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-6-[(1-pyrrolidinyl)ethylamino]-2-pyrimidinyl]amino]benzonitrile hydrochloride (1:1) (50.6%); mp. 208–210° C. (comp. 47).

EXAMPLE B16

To a pressure vessel was added 4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-6-chloro-2-pyrimidinyl]amino] benzonitrile (0.00064 mol), tetrahydrofuran (3 ml), O-methylhydroxylamine (0.06 g), tetrahydrofuran and NaOH 1N (0.00067 mol). The reaction mixture was stirred for 3 days at room temperature, then for 1 day at 75° C., for 1 day at 90° C. and for 2 days at 110° C. To O-methylhydroxylamine (0.60 g) was added tetrahydrofuran (4 ml) and NaOH 50% (0.00719 mol). The liquid was decanted into the reaction flask and the reaction mixture was heated at 110° C. for 3 days. The solvent was evaporated. The residue was dissolved in CH_2Cl_2, washed with a saturated $NaHCO_3$ solution and water, dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH_3CN, filtered off and dried, yielding 0.15 g of 4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-6-(methoxyamino)-2-pyrimidinyl]amino]-benzonitrile (51%); mp. 185–186° C. The sample was dried (0.2 mm Hg, 80° C., 16 hours) (comp. 48).

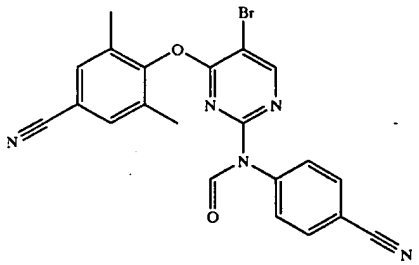
EXAMPLE B17

a) n-Butyllithium (2.0 1, 0.005 mol) was added to a 0° C. stirred solution of 1-(methylethyl)-2-propanamine (0.70 ml, 0.005 mol) and tetrahydrofuran (300 ml). After stirring cold for 30 min, compound (17) (0.005 mol) was added. The resulting mixture was stirred cold for 30 min at which point 1,1-dimethylethyl bromoacetate (1.5 ml, 10 mmol) was added and the temperature was allowed to rise to room temperature and the reaction was stirred for three. In a separate flask n-butyllithium (2.0 ml, 5 mmol) was added to a stirred 0° C. solution of 1-(methylethyl)-2-propanamine (0.70 ml, 5 mmol) in tetrahydrofuran (50 ml) and allowed to react for 30 min at which time it was transferred to the room temperature reaction. This procedure was repeated. Quenched with 0.5 ml H_2O, the sample was concentrated by rotary evaporation onto silica gel, and purified by flash chromatography (eluting with 0, 10, 20% ethylacetate in hexanes) to give a white solid of



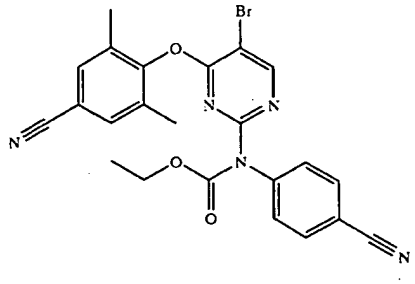
mp. 195–197° C. (comp. 56).

b) A suspension of compound (17) in 40 ml of N,N-dimethylformamide was treated with 0.24 g of NaH. The effervescent mixture was stirred for 90. A solution of 1,4-dichloro-1,4-butanedione in 10 ml N,N-dimethylformamide was prepared and cooled in an ice bath. The mixture prepared from compound (17) was transferred to the cold solution of 1(methylethyl)-1-propanamine and was warmed to room temperature with stirring for 42 hours. Another 0.24 g of NaH was added, the reaction was stirred for 3 days, and diluted with ether and poured into ice. Precipitation was removed by filtration. The 2 phase filtrate was separated and the acidic aqueous fraction was extracted twice more with ether. The combined ether fractions were washed with small volumes of distilled water and dried. The solvent was evaporated and the residue was subjected to silica gel column chromatography. Reverse phase prep HPLC with immediate cooling for lyophilization of the appropriate fractions provided 0.07 g of



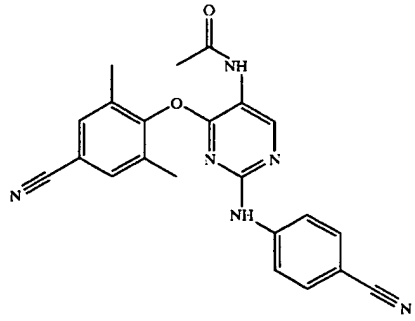
(7.8%); mp. 232–233° C. (comp. 57).

c) To a flask under argon was added NaH 60% and tetrahydrofuran. The reaction was stirred at room temperature for 10 min and compound (17) added. After stirring for 1 hr ethyl carbonochloridate was added. The reaction mixture was stirred at room temperature for another 16 hrs and the solvent evaporated. The residue was partially dissolved in dimethylsulfoxide and filtered. The filtrate was purified by reverse phase chromatography and lyophilized to give 0.47 g (18%) of



(comp. 58).

d) A mixture of of 4-[[5-amino-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]-amino]benzonitrile (0.00147 mol) in ethanoic acid anhydride (10 ml) and 2-propanone (10 ml) was stirred at room temperature for 16 hours. The mixture was then heated to 55° C., and more ethanoic acid anhydride (3 ml) was added. The mixture was removed from heat after 18 hours and stirred for 6 days at room temperature. The sample was concentrated by rotary evaporation to a solid. Purification by column chromatography (eluting with 0, 0.5, 1, 1.5, 2% (10% NH_4OH in CH_3OH) in methylene chloride) yielded



mp. 290–295° C. The solid was dried in vacuo for 16 hours at 60° C. (comp. 49).

EXAMPLE B18

A mixture of 4-[[4-(4-cyano-2,6-dimethylphenoxy)-5-nitro-2-pyrimidinyl]amino]-benzonitrile (0.0005 mol) in tetrahydrofuran (20 ml) was hydrogenated overnight with Pd/C 10% (0.100 g) as a catalyst. After uptake of H_2 (3 equiv; 0.0015 mol), the catalyst was filtered off and the filtrate was concentrated by rotary evaporation and dried in vacuo over 16 hours at 40° C., yielding 0.15 g of 4-[[5-amino-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino] benzonitrile (84%); mp. >300° C. (comp. 50).

EXAMPLE B19

4-[[4-[(2,4,6-trimethylphenyl)amino]-5-nitro-2-pyrimidinyl]amino]benzonitrile (0.001 mol), Pd/C 10% (0.025 g), ethanol (20 ml), and hydrazine (0.030 mol) were combined to form a slurry and stirred at room temperature for 16 hours. The solvent was removed by rotary evaporation. The residue was taken up in tetrahydrofuran (20 ml) and methanol (1 ml). A second portion of hydrazine (0.5 g) was added, and the reaction was stirred for 16 hours at room temperature. A third portion of hydrazine (0.5 ml) was added and the reaction was stirred for an additional 16 hours at room temperature. The sample was concentrated by rotary evaporation onto silica gel (1 g) and purified by flash chromatography (eluent: 0.5, 1,2% 10% (NH_4OH in CH_3OH) in CH_2Cl_2). The desired fractions were purified by preparatory HPLC to yield 0.24 g of 4-[[5-amino-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (70%); mp. 224–225° C. (comp. 51).

EXAMPLE B20

Compound (3) (0.001 mol), trimethyl silanecarbonitrile (0.0012 mol), $Pd(PPh_3)_2Cl_2$ (0.020 g), CuI (0.010 g) and CF_3COOH/H_2O (3 ml) were combined in a sealed tube and heated to 110° C. for 10 hours. Second portions of the catalysts $Pd(PPh_3)_2Cl_2$ (0.020 g) and CuI (0.010 g), and CF_3COOH/H_2O (3 ml) were added and the reaction mixture was stirred for 10 hours at 110° C. The material was concentrated by rotary evaporation. The residue was purified by preparative reversed-phase HPLC. The desired fractions were concentrated and purified by reversed-phase preparative HPLC and dried with a stream of N_2, then in vacuo at 40° C. for 16 hours. Yield: 0.011 g of 4-[[5-ethynyl-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino] benzonitrile; mp. 165–175° C. (comp. 52).

EXAMPLE B21

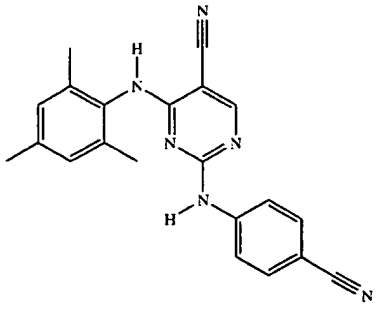
Compound (3) (0.000906 mol), tributylphenyl stannane (0.000906 mol), $Pd(PPh_3)_4$ (0.002718 mol), and 1,4-dioxane (3 ml) were combined under N_2 in a sealed tube and heated to 110° C. for 16 hours. The reaction mixture was cooled and concentrated by rotary evaporation. The sample was purified by Preparatory Reverse Phase HPLC, then dried under Ar stream. Drying in vacuo yielded 0.0845 g of or 4-[[5-phenyl-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino] benzonitrile; mp. 209–214° C. (comp. 53).

EXAMPLE B22

Compound (3) (0.001 mol), tetraethenyl stannane (0.22 ml), 1,4-dioxane (2 ml) and $Pd(PPh_3)_4$ (0.112 g) were combined in a sealed tube under Ar. The mixture was stirred and heated to 100° C. for 16 hours. More tetraethenyl stannane and $Pd(PPh_3)_4$ were added. The reaction was placed under Ar, stirred and heated. The reaction was concentrated by rotary evaporation and purified on preparative HPLC. The material was dried with a N_2 stream, and dried under vacuum for 4 hours at 60° C. to obtain 0.422 g of 4-[[5-ethenyl-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile; mp. 237–242° C. (comp. 54).

EXAMPLE B23

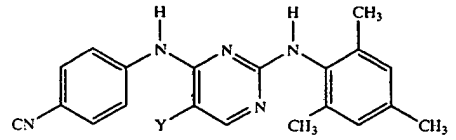
Compound (3) (0.001225 mol), CuCN (0.001470 mol) and N,N-dimethylformamide (2 ml) were combined in a sealed tube under Argon, then stirred and heated to 160° C. for 16 hours. The residue was purified by column chromatography (eluent: CH_2Cl_2/hexane 1/1, then pure CH_2Cl_2). The desired fractions were collected and the solvent was evaporated. The residue was triturated under CH_2Cl_2 at room temperature. The solid was dried (vacuum, 40° C., 24 hours, yielding 0.0864 g of



(24%); mp. 254–259° C. (comp.55).

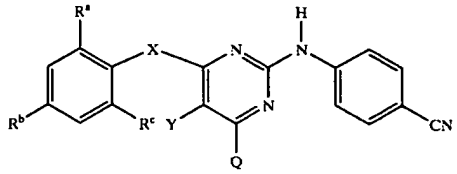
Tables 1, 2, 3 and 4 list compounds of formula (I-a) which were made analogous to one of the above examples.

TABLE 1



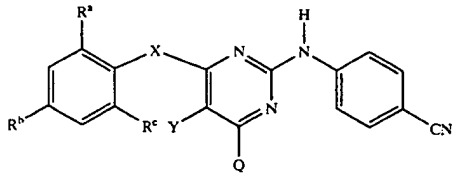
Comp. No.	Ex. No.	Y	Physical data
1	B1a	Cl	—
2	B1a	Br	mp. 227–228° C.
22	B11	NO_2	mp. 224–226° C.

TABLE 2



Co. No.	Ex. No.	R^a	R^b	R^c	X	Y	Q	mp./salt
3	B1b	CH_3	CH_3	CH_3	NH	Br	H	mp. 227–228° C.
4	B2	CH_3	CH_3	CH_3	NH	Cl	NH_2	mp. 241–242° C.; trifluoroacetate (1:1)
5	B3	CH_3	CH_3	CH_3	NH	Cl	H	mp. 224–226° C.
6	B5	CH_3	CH_3	CH_3	O	Cl	H	mp. 218–219° C.
7	B5	CH_3	CH_3	CH_3	S	Cl	H	mp. 264–266° C.
8	B5	CH_3	Br	CH_3	O	Cl	H	mp. 237–238° C.
9	B3	CH_3	Br	CH_3	NH	Cl	H	mp. 217–219° C.
10	B4	Br	CH_3	Br	NH	Cl	H	mp. 262–263° C.
11	B4	Br	Br	F	NH	Cl	H	mp. 200–202° C.
12	B4	CH_3	$C(CH_3)_3$	CH_3	NH	Cl	H	mp. 214–215° C.
13	B4	CH_3	CN	CH_3	NH	Cl	H	mp. 281–283° C.
14	B4	Cl	Cl	CH_3	NH	Cl	H	mp. 243–245° C.
15	B5	Cl	Br	CH_3	O	Cl	H	mp. 244–247° C.
16	B5	CH_3	Cl	CH_3	O	Cl	H	mp. 232–235° C.
17	B6	CH_3	CN	CH_3	O	Br	H	mp. 288–289° C.
18	B5	CH_3	CN	CH_3	O	Cl	H	mp. 283–284° C.
19	B7	CH_3	CN	CH_3	NH	Cl	NH_2	mp. 266–268° C.; trifluoroacetate (1:1)
20	B3	Cl	Cl	CH_3	NH	Br	H	mp. 253–254° C.
21	B3	CH_3	Br	CH_3	NH	Br	H	mp. 243–245° C.
23	B23	CH_3	CN	CH_3	NH	CN	H	mp. 275–290° C.; trifluoroacetate (1:1)
24	B23	CH_3	Br	CH_3	NH	CN	H	mp. 291–299° C.
25	B14	CH_3	CN	CH_3	O	Br	NH—CH_3	mp. 248–250° C.
26	B14	CH_3	CN	CH_3	O	Br	NH_2	mp. 255–256° C.
27	B14	CH_3	CH_3	CH_3	O	Br	NH_2	—
28	B14	CH_3	CH_3	CH_3	O	Br	NH—CH_3	mp. 213–214° C.
29	B14	CH_3	CN	CH_3	O	Br	NH—C_2H_5	mp. 263–264° C.
30	B14	CH_3	CN	CH_3	O	Cl	NH_2	mp. 272–274° C.
31	B14	CH_3	CH_3	CH_3	O	Cl	NH_2	mp. 199–202° C.
32	B11	CH_3	CH_3	CH_3	NH	NO_2	H	mp. >300° C.
33	B5	CH_3	CH_3	CH_3	O	Br	H	mp. 207–215° C.
34	B5	CH_3	CH_3	CH_3	O	Cl	Cl	mp. 225–226° C.
35	B5	CH_3	CN	CH_3	O	Cl	Cl	mp. 273–276° C.
36	B6	CH_3	CN	CH_3	O	Cl	Br	mp. 281–282° C.
37	B5	CH_3	CH_3	CH_3	O	Cl	Br	mp. 214–215° C.
40	B8	CH_3	$CH(CH_3)_2$	CH_3	NH	Br	H	mp. 198° C.; trifluoroacetate (1:2)
41	B10	CH_3	CH_3	CH_3	NH	Br	Cl	mp. 220° C.
42	B9	CH_3	CN	CH_3	NH	Br	Cl	mp. 259° C.

TABLE 2-continued



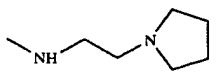
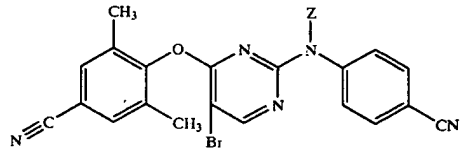
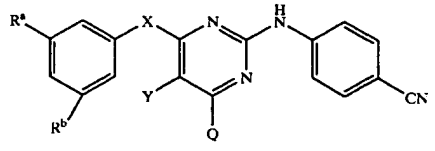
Co. No.	Ex. No.	R^a	R^b	R^c	X	Y	Q	mp./salt
43	B11	CH_3	CN	CH_3	O	NO_2	H	mp. >300° C.
44	B12	CH_3	CN	CH_3	O	Br	CH_3	mp. 260° C.
45	B13	CH_3	CN	CH_3	NH	Br	H	mp. 277° C.
46	B14	CH_3	CN	CH_3	O	Br	NH_2	mp. 255° C.
47	B15	CH_3	CN	CH_3	O	Br		mp. 208° C.; HCl (1:1)
48	B16	CH_3	CN	CH_3	O	Br	—NH—O—CH_3	mp. 185–186° C.
49	B17d	CH_3	CN	CH_3	O	—NH—$COCH_3$	H	mp. 290–295° C.
50	B18	CH_3	CN	CH_3	O	—NH_2	H	mp. >300° C.
51	B18	CH_3	CH_3	CH_3	NH	—NH_2	H	mp. 224–225° C.; trifluoroacetate (1:1)
52	B20	CH_3	CH_3	CH_3	NH	CN	H	mp. 165–175° C.
53	B21	CH_3	CH_3	CH_3	NH	phenyl	H	mp. 209–214° C.
54	B22	CH_3	CH_3	CH_3	NH	—CH=CH_2	H	mp. 237–242° C.; trifluoroacetate (1:1)
55	B23	CH_3	CH_3	CH_3	NH	—CH=CH_2	H	mp. 254–259° C.

TABLE 3



Comp. No.	Ex. No.	Z	
38	B17C	—C(=O)—CH_3	mp. 194–196° C.
56	B17a	—CH_2—CO—O—$C(CH_3)_3$	mp. 195–197° C.
57	B17b	—CH=O	mp. 232–233° C.
58	B17c	—CO—O—C_2H_5	mp. 209–210° C.
59	B6b	—CH_2—CO—OC_2H_5	mp. 185–190° C.
60	B6c	—CH_2—O—CO—$C(CH_3)_3$	mp. 168–169° C.
61	B6d	—CO—CH_2—OCH_2—CO—OCH_3	mp. 184–185° C.

TABLE 4



Comp. No.	Ex. No.	R^a	R^b	X	Y	Q	
39	B5	Cl	Cl	S	Br	H	mp. 198–200° C.

C. Pharmacological Example

EXAMPLE C.1

A rapid, sensitive and automated assay procedure was used for the in vitro evaluation of anti-HIV agents. An HIV-1 transformed T4-cell line, MT-4, which was previously shown (Koyanagi et al., *Int. J. Cancer*, 36, 445–451, 1985) to be highly susceptible to and permissive for HIV infection, served as the target cell line. Inhibition of the HIV-induced cytopathic effect was used as the end point. The viability of both HIV- and mock-infected cells was assessed spectrophotometrically via the in situ reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). The 50% cytotoxic concentration (CC_{50} in μM) was defined as the concentration of compound that reduced the absorbance of the mock-infected control sample by 50%. The percent protection achieved by the compound in HIV-infected cells was calculated by the following formula:

$$\frac{(OD_T)_{HIV} - (OD_C)_{HIV}}{(OD_C)_{MOCK} - (OD_C)_{HIV}} \text{ expressed in \%.}$$

whereby $(OD_T)_{HIV}$ is the optical density measured with a given concentration of the test compound in HIV-infected cells; $(OD_C)_{HIV}$ is the optical density measured for the control untreated HIV-infected cells; $(OD_C)_{MOCK}$ is the optical density measured for the control untreated mock-infected cells; all optical density values were determined at 540 nm. The dose achieving 50% protection according to the above formula was defined as the 50% inhibitory concentration (IC_{50} in μM). The ratio of CC_{50} to IC_{50} was defined as the selectivity index (SI). The compounds of formula (I-A) were shown to inhibit HIV-1 effectively. Particular IC_{50}, CC_{50} and SI values are listed in Table 5 hereinbelow.

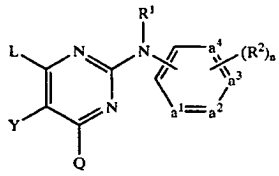
TABLE 5

Co. No.	IC_{50} (μM)	CC_{50} (μM)	SI	Co. No.	IC_{50} (μM)	CC_{50} (μM)	SI
2	0.030	82.6	2730	10	0.005	0.4	92
3	0.006	4.4	738	11	0.002	0.4	183
1	0.004	10.9	2787	12	0.020	48.5	2393
4	0.002	10.0	5555	13	0.0005	0.4	860
5	0.002	0.4	178	14	0.002	0.4	191
6	0.009	>100	>11049	15	0.010	>100	>9661
7	0.084	>100	>1182	16	0.010	>100	>10416
8	0.012	>100	>8298	17	0.002	>10	>6451
9	0.003	1.2	376	18	0.001	>10	>7142
46	0.002	>200	>71428	60	0.002	74.52	39223
61	0.002	>100	>52631				

What is claimed is:

1. A method of treating subjects suffering from HIV (Human Immunodeficiency Virus) infection comprising administering to the subject a therapeutically effective amount of a compound of formula:

(I)



a N-oxide, a pharmaceutically acceptable addition salt, or a stereochemically isomeric form thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula:

—CH=CH—CH=CH— (a-1);

—N=CH—CH=CH— (a-2);

—N=CH—N=CH— (a-3);

—N=CH—CH=N— (a-4);

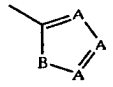
—N=N—CH=CH— (a-5);

n is 0, 1, 2, 3 or 4; and in case $-a^1=a^2-a^3=a^4-$ is (a-1), then n may also be 5;

R^1 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $—C(=O)R^6$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $—S(=O)_pR^6$, —NH—$S(=O)_pR^6$, $—C(=O)R^6$, —NHC(=O)H, —C(=O)$NHNH_2$, $—NHC(=O)R^6$, $—C(=NH)R^6$ or a radical of formula:

(c)



wherein each A independently is N, CH or CR^6;

B is NH, O, S or NR^6;

p is 1 or 2; and

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

C_{3-7}cycloalkyl,

indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, amino carbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,

phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is $—X—R^3$ wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is $—NR^1—$, —NH—NH—, —N=N—, —O—, —C(=O)—, —CHOH—, —S—, —S(=O)— or $—S(=O)_2—$;

Q represents hydrogen, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl or $—NR^4R^5$; and

R^4 and R^5 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl,

polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$, aryl and Het; or

R^4 and R^5 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, or mono- or di(C_{1-12}alkyl)aminoC_{1-4}alkylidene;

Y represents hydroxy, halo, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or $-C(=O)R^6$, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or aryl;

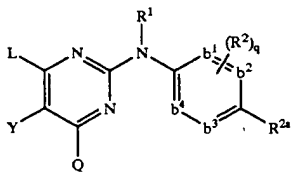
aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhaloC_{1-6}alkyloxy;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidmyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

2. The method of claim 1, wherein R^1 is hydrogen, aryl, formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, or C_{1-6}alkyloxycarbonyl.

3. A method of treating non-nucleoside reverse transcriptase inhibitor resistant HIV infection in a subject in need thereof comprising administering to the subject an effective amount of a compound having the formula:

(I-a)



a N-oxide, an addition salt, or a stereochemically isomeric form thereof, wherein

$-b^1=b^2-C(R^{2a})=b^3-b^4=$ represents a bivalent radical of formula:

$-CH=CH-C(R^{2a})=CH-CH=$ (b-1);

$-N=CH-C(R^{2a})=CH-CH=$ (b-2);

$-CH=N-C(R^{2a})=CH-CH=$ (b-3);

$-N=CH-C(R^{2a})=N-CH=$ (b-4);

$-N=CH-C(R^{2a})=CH-N=$ (b-5);

$-CH=N-C(R^{2a})=N-CH=$ (b-6);

$-N=N-C(R^{2a})=CH-CH=$ (b-7);

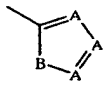
q is 0, 1, 2; or where possible q is 3 or 4;

R^1 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

R^{2a} is cyano, aminocarbonyl, mono- or dimethylaminocarbonyl, C_{1-6}alkyl substituted with cyano, aminocarbonyl or mono- or dimethylaminocarbonyl, C_{2-6}alkenyl substituted with cyano, or C_{2-6}alkynyl substituted with cyano;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $-C(=O)R^6$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or a radical of formula:

(c)



wherein each A independently is N, CH or CR^6;

B is NH, O, S or NR^6;

p is 1 or 2; and

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

C_{3-7}cycloalkyl,

indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,

phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is $-X-R^3$ wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is $-NR^1-$, $-NH-NH-$, $-N=N-$, $-O-$, $-C(=O)-$, $-CHOH-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;

Q represents hydrogen, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl or $-NR^4R^5$; and

R^4 and R^5 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-}

12alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$, aryl and Het; or

R^4 and R^5 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, or mono- or di(C_{1-12}alkyl)aminoC_{1-4}alkylidene;

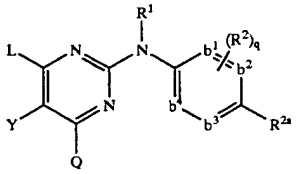
Y represents hydroxy, halo, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or $-C(=O)R^6$, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl) amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or aryl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhaloC_{1-6}alkyloxy;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

4. A method of treating non-nucleoside reverse transcriptase inhibitor resistant HIV-1 infection in a subject in need thereof comprising administering to the subject an effective amount of a compound having the formula:

(I-a)



a N-oxide, an addition salt, or a stereochemically isomeric form thereof, wherein

$-b^1=b^2-C(R^{2a})=b^3-b^4=$ represents a bivalent radical of formula:

$-CH=CH-C(R^{2a})=CH-CH=$ (b-1);

$-N=CH-C(R^{2a})=CH-CH=$ (b-2);

$-CH=N-C(R^{2a})=CH-CH=$ (b-3);

$-N=CH-C(R^{2a})=N-CH=$ (b-4);

$-N=CH-C(R^{2a})=CH-N=$ (b-5);

$-CH=N-C(R^{2a})=N-CH=$ (b-6);

$-N=N-C(R^{2a})=CH-CH=$ (b-7);

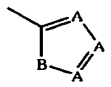
q is 0, 1, 2; or where possible q is 3 or 4;

R^1 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

R^{2a} is cyano, aminocarbonyl, mono- or dimethylaminocarbonyl, C_{1-6}alkyl substituted with cyano, aminocarbonyl or mono- or dimethylaminocarbonyl, C_{2-6}alkenyl substituted with cyano, or C_{2-6}alkynyl substituted with cyano;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $-C(=O)R^6$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl) amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or a radical of formula:

(c)



wherein each A independently is N, CH or CR^6;

B is NH, O, S or NR^6;

p is 1 or 2; and

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

C_{3-7}cycloalkyl,

indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,

phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is $-X-R^3$ wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is $-NR^1-$, $-NH-NH-$, $-N=N-$, $-O-$, $-C(=O)-$, $-CHOH-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;

Q represents hydrogen, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl or $-NR^4R^5$; and

R^4 and R^5 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy,

C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$, aryl and Het; or

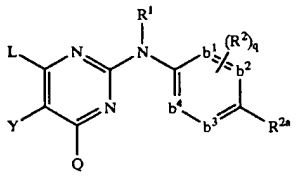
R^4 and R^5 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, or mono- or di(C_{1-12}alkyl)aminoC_{1-4}alkylidene;

Y represents hydroxy, halo, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or $-C(=O)R^6$, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or aryl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhaloC_{1-6}alkyloxy;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

5. A method of treating subjects suffering from HIV (Human Immunodeficiency Virus) infection comprising administering to the subject a therapeutically effective amount of a compound of formula:



(I-a),

a N-oxide, an addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein

$-b^1=b^2-C(R^{2a})=b^3-b^4=$ represents a bivalent radical of formula:

$-CH=CH-C(R^{2a})=CH-CH=$ (b-1);

$-N=CH-C(R^{2a})=CH-CH=$ (b-2);

$-CH=N-C(R^{2a})=CH-CH=$ (b-3);

$-N=CH-C(R^{2a})=N-CH=$ (b-4);

$-N=CH-C(R^{2a})=CH-N=$ (b-5);

$-CH=N-C(R^{2a})=N-CH=$ (b-6);

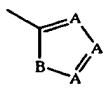
$-N=N-C(R^{2a})=CH-CH=$ (b-7);

q is 0, 1, 2; or where possible q is 3 or 4;

R^1 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

R^{2a} is cyano, aminocarbonyl, mono- or di(methyl)aminocarbonyl, C_{1-6}alkyl substituted with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl, C_{2-6}alkenyl substituted with cyano, or C_{2-6}alkynyl substituted with cyano;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $-C(=O)R^6$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or a radical of formula:



(c)

wherein each A independently is N, CH or CR^6;

B is NH, O, S or NR^6;

p is 1 or 2; and

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

C_{3-7}cycloalkyl,

indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,

phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is $-X-R^3$ wherein

R^3 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

X is $-NR^1-$, $-NH-NH-$, $-N=N-$, $-O-$, $-C(=O)-$, $-CHOH-$, $-S-$, $-S(=O)-$ or $-S(=O)_2-$;

Q represents hydrogen, C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl or $-NR^4R^5$; and

R^4 and R^5 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, ammo, imino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$, aryl and Het; or

R^4 and R^5 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}alkylidene;

Y represents hydroxy, halo, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or $-C(=O)R^6$, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl) amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or aryl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl and polyhalo C_{1-6}alkyloxy;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

* * * * *

Exhibit 4

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Patent Maintenance Fees		03/07/2008 11:39 AM EST	
Patent Number:	7037917	**Application Number:**	10634682
Issue Date:	05/02/2006	**Filing Date:**	08/05/2003
Window Opens:	05/04/2009	**Surcharge Date:**	11/03/2009
Window Closes:	05/03/2010	**Payment Year:**	
Entity Status:	LARGE		
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City:	NEW BRUNSWICK		
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Zip Code:	089337003		
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Currently there are no fees due.			

Exhibit 5

Terminal Disclaimers filed in U.S. Patent No. 7,037,917

Docket No. JAB-1425-USCNT1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	De Corte B., et al.	Confirmation No.:	7134
Appln. No.	:	10/634,682		
Filed	:	08/05/2003		
Title	:	HIV REPLICATION INHIBITING PYRIMIDINES		
Art Unit	:	1624		
Examiner	:	Venkataraman Balasubramanian		

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

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(Date of Deposit)

Laura A. Donnelly
(Name of applicant, assignee, or Registered Representative)

/Laura A. Donnelly/
(Signature)

June 9, 2005
(Date of Signature)

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P.O. Box 1450
Alexandria, VA 22313-1450

TERMINAL DISCLAIMER

Dear Sir:

The owner, Janssen Pharmaceutica N.V., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any claim of similar scope to claim 21 (i.e., a method of treating subjects suffering from HIV comprising

administering the compounds identified therein) in any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term of prior patent No. 6,878,717 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any such claim of any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any such claim of any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:

expires for failure to maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued, or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

In addition, in making the above disclaimer, the owner does not disclaim the terminal part of the term of any of the claims not of similar scope to claim 21, including, but not limited to, the remaining claims now pending in the instant application.

Check either box 1 or 2 below, if appropriate:

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

2. ☒ The undersigned is an attorney or agent of record.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

By: /Laura A. Donnelly/
Laura A. Donnelly
Reg. No. 38,435

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-1729
Dated: June 9, 2005

☒ The Terminal Disclaimer fee of $130.00 and any additional fees which may be owed in connection with the filing of this Terminal Disclaimer can be charged to Johnson & Johnson Deposit Account No. 10-0750/JAB-1425-USCNT1/LAD. Three copies of this sheet are enclosed.

Docket No. JAB-1425-USCNT1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: De Corte B., et al.	Confirmation No.:	7134
Appln. No.	: 10/634,682		
Filed	: 08/05/2003		
Title	: HIV REPLICATION INHIBITING PYRIMIDINES		
Art Unit	: 1624		
Examiner	: Venkataraman Balasubramanian		

CERTIFICATION UNDER (37 C.F.R. § 1.8(A)

I hereby certify that, on the date shown below, this correspondence is being:

Mailing

☐ deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date: August 2, 2005

Facsimile

☒ transmitted by facsimile to the United States Patent and Trademark Office at (571) 273-8300.

Signature: Laura C. Donnelly

Laura A. Donnelly

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TERMINAL DISCLAIMER

Dear Sir:

The owner, Janssen Pharmaceutica N.V., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any claim in any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term of prior patent No. 6,878,717 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any such claim of any patent so granted on the instant

application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any such claim of any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:

expires for failure to maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued, or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate:

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

2. ☒ The undersigned is an attorney or agent of record.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

By: Laura C. Donnelly

Laura A. Donnelly
Reg. No. 38,435

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-1729
Dated: August 2, 2005

☒ The Terminal Disclaimer fee of $130.00 and any additional fees which may be owed in connection with the filing of this Terminal Disclaimer can be charged to Johnson & Johnson Deposit Account No. 10-0750/JAB-1425-USCNT1/LAD. Three copies of this sheet are enclosed.

PTO/SB/ 44 (04-04)
Approved for use through 04/30/2007. OMB 0651-0033
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,037,917
DATED : May 2, 2006
INVENTOR(S) : De Corte et al.

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Item (75), please add the following inventor:

-- Koenraad Jozef, Lodewijk, Marcel Andries, Beerse (BE)--

Column 38, line 9, claim 22, change "a an" to --an--.

Column 38, line 15, claim 24, change "pyriniidinyl" to --pyrimidinyl--.

Column 38, line 28, claim 28, change "1" to --27--.

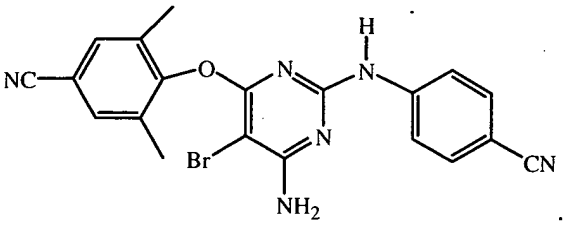
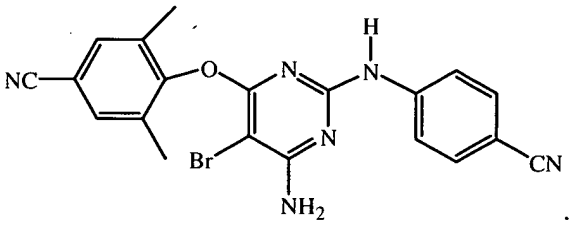
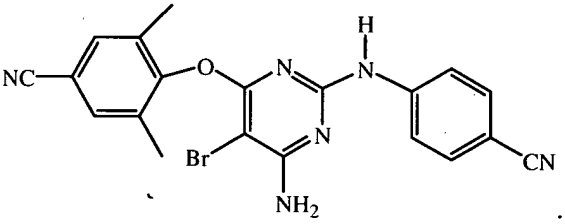
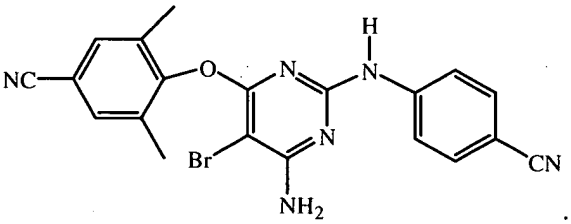
MAILING ADDRESS OF SENDER:
Philip S. Johnson
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003

PATENT NO. 7,037,917

No. of additional copies

Exhibit 7

Claims 1-5, 9, 11, 15, 21, 22, and 26-32 of U.S. Patent No. 7,037,917 Claim the Active Ingredient of the Approved Product

1. A pyrimidinyl compound 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl] amino]benzonitrile, a N-oxide, an addition salt, a quaternary amine or a stereochemically isomeric form thereof, said compound having the following structure: 	The IUPAC name for etravirine is 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]benzonitrile and the chemical structure of etravirine is: 
2. A pyrimidinyl compound wherein the pyrimidinyl compound is 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]benzonitrile, said compound having the following structure: 	The IUPAC name for etravirine is 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenyloxy)-2-pyrimidinyl]amino]benzonitrile and the chemical structure of etravirine is: 
3. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a pyrimidinyl compound according to any of claims 1 or 2.	Etravirine is to be employed in the form of a pharmaceutical composition as a tablet comprising etravirine and one or more pharmaceutically acceptable carriers.

4. A combination comprising a pyrimidinyl compound according to any of claims 1 or 2 and an antiretroviral compound, wherein said antiretroviral compound comprises at least one of a nucleoside reverse transcriptase inhibitor, a non-nucleoside reverse transcriptase inhibitor, a TIBO compound, an α-APA compound, a TAT-inhibitor, a protease inhibitor, an immunomodulating agent, and mixtures thereof.	Etravirine is to be co-administered with another antiretroviral compound, including, e.g., a nucleoside reverse transcriptase inhibitor.
5. A combination according to claim 4, wherein said nucleoside reverse transcriptase inhibitor comprises at least one of zidovudine (3'-azido-3'-deoxythymidine, AZT), didanosine (dideoxy inosine; ddI), zalcitabine (dideoxycytidine, ddC), lamivudine (3'-thia-2'-3'-dideoxycytidine, 3TC), and mixtures thereof.	Etravirine is to be co-administered with another antiretroviral compound, including, e.g., a nucleoside reverse transcriptase inhibitor such as zidovudine.
9. A combination according to claim 4, wherein said protease inhibitor comprises at least one of indinavir, ritanovir, saquinovir, ABT-378, and mixtures thereof.	Etravirine is to be co-administered with another antiretroviral compound, including, e.g., a protease inhibitor such as ritanovir.
11. A combination according to claim 5, further comprising a pharmaceutically acceptable carrier.	Etravirine and the another antiretroviral compound are to be employed in pharmaceutically acceptable carriers.
15. A combination according to claim 9, further comprising a pharmaceutically acceptable carrier.	Etravirine and the another antiretroviral compound are to be employed in pharmaceutically acceptable carriers.
21. A method of treating subjects suffering from HIV (Human Immunodeficiency Virus) infection comprising administering to the subject an effective amount of a compound according to claims 1 or 2.	Etravirine is indicated for the treatment of HIV infection.
22. A method of treating subjects suffering from HIV (Human Immunodeficiency Virus) infection comprising administering to the subject an effective amount of a combination according to claim 4.	Etravirine is indicated in combination with other antiretroviral agents for the treatment of HIV.
26. A pharmaceutical composition as claimed in	Etravirine is to be in tablet form.

claim 3, wherein the pharmaceutical composition is a tablet.	
27. A pharmaceutical composition as claimed in claim 3, wherein the effective amount is between 1 to 1000 mg of active ingredient per unit dosage form.	Etravirine is to be in a 100 mg dosage form.
28. A pharmaceutical composition as claimed in claim 27, wherein the effective amount is between 5 and 200 mg of active ingredient per unit dosage form.	Etravirine is to be in a 100 mg dosage form.
29. A tablet as claimed in claim 26, wherein the effective amount is between 1 to 1000 mg of active ingredient.	Etravirine is to be in a 100 mg tablet dosage form.
30. A tablet as claimed in claim 29, wherein the effective amount is between 5 to 200 mg of active ingredient.	Etravirine is to be in a 100 mg tablet dosage form.
31. A method of treating subjects suffering from HIV-1 (Human Immunodeficiency Virus) infection that have acquired resistance to art-known non-nucleoside reverse transcriptase inhibitors comprising administering to the subject an effective amount of a compound according to any of claims 1 or 2.	Etravirine is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients, including those with NNRTI resistance.
32. A method of treating subject suffering from HIV-1 (Human Immunodeficiency Virus) infection that have acquired resistance to art-known non-nucleoside reverse transcriptase inhibitors comprising administering to the subject an effective amount of a combination comprising a pyrimidinyl compound according to any of claims 1 or 2 and an antiretroviral compound, wherein said antiretroviral compound comprises at least one of a nucleoside reverse transcriptase inhibitor, a non-nucleoside reverse transcriptase inhibitor, a TIBO compound, an α-APA compound, a TAT-inhibitor, a protease	Etravirine is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients, including those with NNRTI resistance. Etravirine is to be co-administered with other antiretroviral agents.

inhibitor, an immunomodulating agent, and mixtures thereof, and wherein said pyrimidinyl compound and said antiretroviral compound are administered simultaneously, separately or sequentially.	

Exhibit 8

DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW

IND 63,146 (INTELENCE™ (etravirine)) US Submission Log

Date	Serial #	Type of Submission
10/31/2001	000	Original Investigational New Drug Application
11/26/2001	001	Information Amendment - Pharmacology/Toxicology
11/26/2001	002	Information Amendment - Pharmacology/Toxicology
1/22/2002	003	IND Safety Report
2/4/2002	004	Meeting Request
2/19/2002	005	Information Amendment – Clinical
3/8/2002	006	Briefing Package April 3, 2002 meeting
3/28/2002	007	Information Amendment - Pharmacology/Toxicology
5/17/2002	008	Sponsor Name & Address Change
6/21/2002	009	Protocol Amendment - Change in Protocol TMC125-C135; Information Amendment - Chemistry/Microbiology, Pharmacology/Toxicology, & Clinical; Response to FDA Request for Information
7/16/2002	010	Draft Protocols for Review
9/25/2002	011	Protocol Amendment - Change in Protocol TMC125-C135
9/25/2002	012	Protocol Amendment - New Protocol TMC125-C144
10/14/2002	013	IND Safety Report
11/6/2002	014	IND Safety Report
11/6/2002	015	General Correspondence
12/18/2002	016	IND Safety Report
1/23/2003	017	General Correspondence
1/23/2003	018	Response to FDA Request for Information
1/24/2003	019	IND Safety Report
2/7/2003	020	Information Amendment - Pharmacology/Toxicology
2/7/2003	021	Annual Report
2/14/2003	022	Investigator Brochure
2/26/2003	023	Response to FDA Request for Information
3/7/2003	024	IND Safety Report
3/25/2003	025	IND Safety Report
6/2/2003	026	Sponsor Name & Address Change
7/14/2003	027	IND Safety Report
8/4/2003	028	Meeting Request
8/18/2003	029	IND Safety Report
8/18/2003	030	IND Safety Report
8/28/2003	031	IND Safety Report
9/5/2003	032	IND Safety Report
9/15/2003	033	Information Amendment - Clinical
9/16/2003	034	Briefing Package - Oct. 14, 2003 Type B Meeting

Date	Serial #	Type of Submission
9/16/2003	035	IND Safety Report
10/1/2003	036	IND Safety Report
10/6/2003	037	Response to FDA Request for Information
10/7/2003	038	Information Amendment - Chemistry/Microbiology
10/24/2003	039	IND Safety Report
11/3/2003	040	IND Safety Report
11/7/2003	041	IND Safety Report
11/7/2003	042	Response to FDA Request for Information
12/8/2003	043	General Correspondence
12/19/2003	044	General Correspondence
1/26/2004	045	IND Safety Report
2/2/2004	046	General Correspondence
2/3/2004	047	GENERAL CORRESPONDENCE-WITHDRAWL OF STUDIES TMC125-C135/TMC125-C144
2/4/2004	048	Information Amendment - Chemistry/Microbiology
2/5/2004	049	IND Safety Report
2/9/2004	050	Annual Report
2/11/2004	051	Protocol Amendment - New Protocol TMC125-C223
2/19/2004	052	IND Safety Report
2/25/2004	053	IND Safety Report
3/15/2004	054	IND Safety Report
3/26/2004	055	Response to FDA Request for Information
4/7/2004	056	IND Safety Report
4/8/2004	057	Investigator Brochure Edition 8
4/21/2004	058	IND Safety Report
4/26/2004	059	IND Safety Report
4/27/2004	060	IND Safety Report
5/10/2004	061	Response to FDA Request for Information
5/12/2004	062	Protocol Amendment - Change in Protocol TMC125-C223
5/19/2004	063	Protocol Amendment - New Investigator TMC125-C223
5/25/2004	064	IND Safety Report
6/1/2004	065	IND Safety Report
6/11/2004	066	IND Safety Report
6/24/2004	067	IND Safety Report
6/29/2004	068	IND Safety Report
6/30/2004	069	Protocol Amendment - New Investigator TMC125-C223
7/6/2004	070	IND Safety Report
7/7/2004	071	IND Safety Report
7/9/2004	072	Protocol Amendment - New Protocol TMC125-C151 & TMC125-C156
7/14/2004	073	IND Safety Report
7/15/2004	074	Protocol Amendment - Change in Protocol TMC125-C223
7/26/2004	075	IND Safety Report

Date	Serial #	Type of Submission
7/27/2004	076	IND Safety Report
7/28/2004	077	Protocol Amendment - New Protocol TMC125-C211
7/29/2004	078	IND Safety Report
8/3/2004	079	IND Safety Report
8/4/2004	080	Protocol Amendment - New Investigator TMC125-C223
8/10/2004	081	IND Safety Report
8/18/2004	082	IND Safety Report
8/25/2004	083	IND Safety Report
8/26/2004	084	Protocol Amendment - New Investigator TMC125-C223
9/2/2004	085	IND Safety Report
9/7/2004	086	IND Safety Report
9/13/2004	087	IND Safety Report
9/16/2004	088	IND Safety Report
9/21/2004	089	Information Amendment - Chemistry/Microbiology
9/21/2004	090	IND Safety Report
9/23/2004	091	IND Safety Report
9/24/2004	092	IND Safety Report
9/30/2004	093	Protocol Amendment- New Protocol TMC125-C141
9/30/2004	094	Information Amendment - Chemistry/Microbiology
10/4/2004	095	Protocol Amendment - New Investigator TMC125-C223
10/6/2004	096	IND Safety Report
10/13/2004	097	IND Safety Report
10/19/2004	098	IND Safety Report
10/22/2004	099	IND Safety Report
10/26/2004	100	IND Safety Report
10/27/2004	101	Protocol Amendment - Change in Protocol TMC125-C223
10/29/2004	102	IND Safety Report
11/12/2004	103	IND Safety Report
11/12/2004	104	Protocol Amendment - New Protocol TMC125-C117
11/17/2004	105	IND Safety Report
11/18/2004	106	IND Safety Report
11/22/2007	107	Information Amendment - Pharmacology/Toxicology
11/23/2004	108	IND Safety Report
12/3/2004	109	IND Safety Report
12/7/2004	110	IND Safety Report
12/8/2004	111	IND Safety Report
12/9/2004	112	IND Safety Report
12/14/2004	113	IND Safety Report
12/15/2004	114	IND Safety Report
12/16/2004	115	IND Safety Report
12/16/2004	116	Response to FDA Request for Information
12/20/2004	117	IND Safety Report

Date	Serial #	Type of Submission
12/23/2004	118	IND Safety Report
12/23/2004	119	Information Amendment - Pharmacology/Toxicology
1/5/2005	120	IND Safety Report
1/7/2005	121	IND Safety Report
1/7/2005	122	Response to FDA Request for Information
1/13/2005	123	General Correspondence
1/13/2005	124	IND Safety Report
1/14/2005	125	Response to FDA Request for Information
1/18/2005	126	IND Safety Report
1/18/2005	127	IND Safety Report
1/19/2005	128	Response to FDA Request for Information
1/19/2005	129	IND Safety Report
1/20/2005	130	IND Safety Report
1/24/2005	131	Protocol Amendment - New Investigator TMC125-C211
1/24/2005	132	IND Safety Report
1/25/2005	133	IND Safety Report
1/26/2005	134	IND Safety Report
1/26/2005	135	Response to FDA Request for Information
1/27/2005	136	IND Safety Report
1/28/2005	137	IND Safety Report
2/2/2005	138	IND Safety Report
2/3/2005	139	IND Safety Report
2/4/2005	140	IND Safety Report
2/8/2005	141	Request for Special Protocol Assessment
2/8/2005	142	Request for Special Protocol Assessment
2/8/2005	143	IND Safety Report
2/9/2005	144	Annual Report
2/10/2005	145	IND Safety Report
2/10/2005	146	Protocol Amendment - Change in Protocol TMC125-C223
2/14/2005	147	IND Safety Report
2/15/2005	148	IND Safety Report
2/16/2005	149	Response to FDA Request for Information
2/17/2005	150	IND Safety Report
2/18/2005	151	Request for Special Protocol Assessment
2/22/2005	152	IND Safety Report
2/23/2005	153	IND Safety Report
2/25/2005	154	Response to FDA Request for Information
2/28/2005	155	IND Safety Report
2/28/2005	156	Meeting Request
3/3/2005	157	IND Safety Report
3/3/2005	158	Protocol Amendment - Change in Protocol TMC125-C211
3/8/2005	159	IND Safety Report

Date	Serial #	Type of Submission
3/10/2005	160	IND Safety Report
3/14/2005	161	IND Safety Report
3/24/2005	162	IND Safety Report
3/28/2005	163	IND Safety Report
4/1/2005	164	Information Amendment - Clinical
4/5/2005	165	IND Safety Report
4/5/2005	166	Protocol Amendment - New Investigator TMC125-C211
4/6/2005	167	IND Safety Report
4/8/2005	168	Briefing Package - May 11, 2005 Type C Meeting
4/12/2005	169	Protocol Amendment - New Protocol TMC125-C229
4/14/2005	170	IND Safety Report
4/15/2005	171	Meeting Request
4/19/2005	172	Protocol Amendment - New Investigator TMC125-C223
4/19/2005	173	IND Safety Report
4/20/2005	174	Response to FDA Request for Information
4/21/2005	175	IND Safety Report
4/25/2005	176	Response to FDA Request for Information
4/26/2005	177	IND Safety Report
4/27/2005	178	IND Safety Report
4/28/2005	179	IND Safety Report
4/29/2005	180	IND Safety Report
5/3/2005	181	IND Safety Report
5/3/2005	182	Information Amendment - Clinical
5/4/2005	183	Response to FDA Request for Information
5/5/2005	184	Information Amendment - Clinical
5/5/2005	185	IND Safety Report
5/6/2005	186	Information Amendment - Clinical
5/10/2005	187	IND Safety Report
5/12/2005	188	IND Safety Report
5/16/2005	189	IND Safety Report
5/17/2005	190	IND Safety Report
5/23/2005	191	Response to FDA Request for Information
5/23/2005	192	Briefing Package - June 17, 2005 Type B Meeting
6/1/2005	193	IND Safety Report
6/10/2005	194	General Correspondence
6/10/2005	195	Response to FDA Request for Information
6/15/2005	196	Response to FDA Request for Information
6/16/2005	197	IND Safety Report
6/22/2005	198	IND Safety Report
6/28/2005	199	Protocol Amendment - New Investigator TMC125-C211
6/28/2005	200	IND Safety Report
7/6/2005	201	IND Safety Report

Date	Serial #	Type of Submission
7/7/2005	202	Response to FDA Request for Information
7/11/2005	203	IND Safety Report
7/11/2005	204	Meeting Request
7/13/2005	205	IND Safety Report
7/13/2005	206	Protocol Amendment - New Investigator TMC125-C229
7/14/2005	207	Information Amendment - Pharmacology/Toxicology
7/18/2005	208	Investigator Brochure Edition 9
7/19/2005	209	Response to FDA Request for Information
7/20/2005	210	Response to FDA Request for Information
7/27/2005	211	IND Safety Report
8/1/2005	212	Investigator Brochure Edition 10
8/2/2005	213	Response to FDA Request for Information
8/2/2005	214	IND Safety Report
8/3/2005	215	IND Safety Report
8/8/2005	216	Briefing Package - Sept. 6, 2005 Type C Meeting
8/9/2005	217	Response to FDA Request for Information
8/10/2005	218	Response to FDA Request for Information
8/11/2005	219	Response to FDA Request for Information
8/11/2005	220	Request for Fast Track Designation
8/12/2005	221	IND Safety Report
8/15/2005	222	IND Safety Report
8/18/2005	223	Protocol Amendment - New Investigator TMC125-C229
8/22/2005	224	Response to FDA Request for Information
8/24/2005	225	IND Safety Report
8/29/2005	226	IND Safety Report
8/30/2005	227	IND Safety Report
8/31/2005	228	Information Amendment - Pharmacology/Toxicology
9/1/2005	229	General Correspondence
9/8/2005	230	IND Safety Report
9/13/2005	231	IND Safety Report
9/16/2005	232	IND Safety Report
9/19/2005	233	IND Safety Report
9/20/2005	234	IND Safety Report
9/20/2005	235	Response to FDA request for information
9/21/2005	236	IND Safety Report
9/22/2005	237	Response to FDA request for information
9/23/2005	238	IND Safety Report
9/23/2005	239	Protocol Amendment - New Investigator TMC125-C229
9/29/2005	240	IND Safety Report
10/7/2005	241	IND Safety Report
10/10/2005	242	IND Safety Report
10/12/2005	243	IND Safety Report

Date	Serial #	Type of Submission
10/19/2005	244	IND Safety Report
10/19/2005	245	Protocol Amendment - New Protocol TMC125-C206 & TMC125-C216
10/19/2005	246	Information Amendment - Chemistry/Microbiology
10/21/2005	247	IND Safety Report
10/25/2005	248	IND Safety Report
10/26/2005	249	Information Amendment - Chemistry/Microbiology
10/27/2005	250	General Correspondence
10/27/2005	251	IND Safety Report
10/28/2005	252	IND Safety Report
10/28/2005	253	Protocol Amendment - New Investigator TMC125-C229
10/31/2005	254	General Correspondence
11/1/2005	255	General Correspondence
11/1/2005	256	Protocol Amendment - Change in Protocol TMC125-C211 & TMC125-C229
11/2/2005	257	IND Safety Report
11/2/2005	258	Information Amendment - Pharmacology/Toxicology
11/3/2005	259	Protocol Amendment - Change in Protocol TMC125-C206 & TMC125-C216
11/7/2005	260	IND Safety Report
11/10/2005	261	IND Safety Report
11/15/2005	262	IND Safety Report
11/18/2005	263	Protocol Amendment - New Protocol TMC125-C227
11/21/2005	264	General Correspondence
11/23/2005	265	IND Safety Report
11/29/2005	266	IND Safety Report
11/29/2005	267	General Correspondence
11/30/2005	268	IND Safety Report
12/1/2005	269	IND Safety Report
12/8/2005	270	IND Safety Report
12/8/2005	271	General Correspondence
12/12/2005	272	Response to FDA Request for Information
12/15/2005	273	IND Safety Report
12/19/2005	274	Protocol Amendment - New Investigator TMC125-C206 & TMC125-C216
12/20/2005	275	Protocol Amendment - New Investigator TMC125-C229
12/22/2005	276	IND Safety Report
12/22/2005	277	Protocol Amendment - New Investigator TMC125-C211
12/22/2005	278	General Correspondence
1/10/2006	279	IND Safety Report
1/12/2006	280	Protocol Amendment - New Investigator TMC125-C223
1/12/2006	281	IND Safety Report
1/12/2006	282	Information Amendment - Pharmacology/Toxicology
1/19/2006	283	IND Safety Report
1/20/2006	284	Information Amendment - Clinical
1/26/2006	285	IND Safety Report

Date	Serial #	Type of Submission
1/30/2006	286	Protocol Amendment - New Investigator TMC125-C211
1/31/2006	287	Information Amendment - Pharmacology/Toxicology
2/3/2006	288	General Correspondence
2/6/2006	289	Protocol Amendment - New Investigator TMC125-C206 & TMC125-C216
2/7/2006	290	IND Safety Report
2/7/2006	291	Annual Report
2/8/2006	292	Draft Protocol for Review
2/16/2006	293	Protocol Amendment - New Investigator TMC125-C223
2/22/2006	294	Protocol Amendment - New Investigator TMC125-C229
2/23/2006	295	IND Safety Report
3/1/2006	296	IND Safety Report
3/1/2006	297	Protocol Amendment - New Investigator TMC125-C211
3/1/2006	298	Information Amendment - Clinical
3/6/2006	299	IND Safety Report
3/6/2006	300	Protocol Amendment - Change in Protocol TMC125-C206 & TMC125-C216
3/7/2006	301	IND Safety Report
3/7/2006	302	General Correspondence
3/9/2006	303	IND Safety Report
3/9/2006	304	Information Amendment - Clinical
3/13/2006	305	IND Safety Report
3/15/2006	306	IND Safety Report
3/15/2006	307	Information Amendment - Pharmacology/Toxicology
3/15/2006	308	Information Amendment - Clinical
3/16/2006	309	IND Safety Report
3/17/2006	310	IND Safety Report
3/23/2006	311	IND Safety Report
3/23/2006	312	IND Safety Report
3/23/2006	313	General Correspondence
3/27/2006	314	IND Safety Report
3/28/2006	315	IND Safety Report
4/4/2006	316	IND Safety Report
4/4/2006	317	Protocol Amendment - New Investigator TMC125-C229
4/4/2006	318	General Correspondence
4/5/2006	319	IND Safety Report
4/5/2006	320	General Correspondence
4/7/2006	321	IND Safety Report
4/10/2006	322	IND Safety Report
4/10/2006	323	Investigator's Brochure Addenda
4/11/2006	324	Information Amendment - Clinical
4/11/2006	325	IND Safety Report
4/14/2006	326	Response to FDA Request for Information
4/18/2006	327	IND Safety Report

Date	Serial #	Type of Submission
4/21/2006	328	Response to FDA Request for Information
4/24/2006	329	IND Safety Report
4/27/2006	330	IND Safety Report
5/1/2006	331	Letter of Authorization - Dr. Bellman
5/1/2006	332	General Correspondence
5/3/2006	333	IND Safety Report
5/3/2006	334	Protocol Amendment - New Protocol, New Investigator TMC125-C217
5/4/2006	335	Protocol Amendment - New Investigator TMC125-C206 & TMC125-C216
5/4/2006	336	IND Safety Report
5/4/2006	337	Response to FDA Request for Information
5/5/2006	338	IND Safety Report
5/9/2006	339	Draft Protocol for Review
5/10/2006	340	IND Safety Report
5/11/2006	341	IND Safety Report
5/12/2006	342	General Correspondence
5/12/2006	343	IND Safety Report
5/16/2006	344	IND Safety Report
5/19/2006	345	Information Amendement - Pharmacology/Toxicology
5/22/2006	346	IND Safety Report
5/24/2006	347	IND Safety Report
5/25/2006	348	IND Safety Report
5/26/2006	349	IND Safety Report
6/2/2006	350	IND Safety Report
6/5/2006	351	Protocol Amendment - New Investigator TMC125-C206 & TMC125-C216
6/7/2006	352	IND Safety Report
6/9/2006	353	Information Amendment - Clinical
6/13/2006	354	IND Safety Report
6/14/2006	355	IND Safety Report
6/15/2006	356	Response to FDA Request for Information
6/16/2006	357	Letter of Authorization - Dr. Schrader
6/16/2006	358	Information Amendment - Clinical
6/19/2006	359	IND Safety Report
6/20/2006	360	Information Amendment - Clinical
6/21/2006	361	IND Safety Report
6/22/2006	362	IND Safety Report
6/23/2006	363	IND Safety Report
6/26/2006	364	IND Safety Report
6/26/2006	365	Information Amendment - Clinical
6/27/2006	366	Informaiton Amendment - Clinical
6/28/2006	367	IND Safety Report
6/28/2006	368	General Correspondence
6/29/2006	369	IND Safety Report

Date	Serial #	Type of Submission
6/30/2006	370	IND Safety Report
7/5/2006	371	IND Safety Report
7/6/2006	372	IND Safety Report
7/10/2006	373	IND Safety Report
7/11/2006	374	IND Safety Report
7/11/2006	375	Protocol Amendment - New Investigator TMC125-C206
7/12/2006	376	IND Safety Report
7/12/2006	377	IND Safety Report
7/18/2006	378	Information Amendment - Clinical
7/19/2006	379	Information Amendment - Clinical
7/20/2006	380	IND Safety Report
7/24/2006	381	IND Safety Report
7/24/2006	382	General Correspondence
7/26/2006	383	IND Safety Report
7/27/2006	384	Information Amendment - Clinical
7/28/2006	385	IND Safety Report
8/3/2006	386	IND Safety Report
8/7/2006	387	IND Safety Report
8/7/2006	388	General Correspondence
8/8/2006	389	IND Safety Report
8/9/2006	390	IND Safety Report
8/9/2006	391	Information Amendment - Clinical
8/9/2006	392	Investigator's Brochure- Edition 11
8/10/2006	393	Information Amendment - Clinical
8/14/2006	394	IND Safety Report
8/17/2006	395	IND Safety Report
8/18/2006	396	Information Amendment - Clinical
8/21/2006	397	IND Safety Report
8/23/2006	398	IND Safety Report
8/24/2006	399	Protocol Amendment - New Investigator TMC125-C229
8/28/2006	400	IND Safety Report
8/29/2006	401	IND Safety Report
8/30/2006	402	IND Safety Report
8/31/2006	403	IND Safety Report
9/1/2006	404	General Correspondence
9/5/2006	405	IND Safety Report
9/7/2006	406	IND Safety Report
9/8/2006	407	IND Safety Report
9/11/2006	408	IND Safety Report
9/12/2006	409	Protocol Amendment - Change in Protocol TMC125-C206 & TMC125-C216
9/13/2006	410	Protocol Amendment - Change in Protocol TMC125-C217
9/14/2006	411	IND Safety Report

Date	Serial #	Type of Submission
9/14/2006	412	Protocol Amendment - New Investigator TMC125-C206 & TMC125-C216
9/15/2006	413	IND Safety Report
9/18/2006	414	IND Safety Report
9/19/2006	415	IND Safety Report
9/20/2006	416	IND Safety Report
9/21/2006	417	Protocol Amendment-Change in Protocol TMC125-C229
9/22/2006	418	IND Safety Report
9/22/2006	419	Information Amendment-Pharmacology/Toxicology
9/22/2006	420	Protocol Amendment-Change in Protocol TMC125-C229
9/25/2006	421	IND Safety Report
9/26/2006	422	IND Safety Report
9/26/2006	423	General Correspondence
9/27/2006	424	Information Amendment - Clinical
9/28/2006	425	IND Safety Report
9/29/2006	426	IND Safety Report
10/3/2006	427	IND Safety Report
10/4/2006	428	IND Safety Report
10/5/2006	429	IND Safety Report
10/6/2006	430	IND Safety Report
10/9/2006	431	IND Safety Report
10/11/2006	432	IND Safety Report
10/13/2006	433	IND Safety Report
10/17/2006	434	IND Safety Report
10/18/2006	435	IND Safety Report
10/19/2006	436	General Correspondence
10/19/2006	437	Protocol Amendment - New Investigator TMC125-C229
10/20/2006	438	IND Safety Report
10/23/2006	439	IND Safety Report
10/24/2006	440	IND Safety Report
10/25/2006	441	IND Safety Report
10/27/2006	442	IND Safety Report
10/30/2006	443	IND Safety Report
10/31/2006	444	IND Safety Report
10/31/2006	445	General Correspondence
11/3/2006	446	Protocol Amendment - New Investigator TMC125-C206
11/7/2006	447	Information Amendment - Clinical
11/8/2006	448	IND Safety Report
11/20/2006	449	General Correspondence
11/21/2006	450	Meeting Request
11/27/2006	451	IND Safety Report
11/27/2006	452	General Correspondence
11/28/2006	453	Draft Protocol for Review

Date	Serial #	Type of Submission
11/30/2006	454	Information Amendment - Clinical
12/5/2006	455	General Correspondence
12/6/2006	456	IND Safety Report
12/11/2006	457	IND Safety Report
12/13/2006	458	IND Safety Report
12/19/2006	459	Information Amendment - Pharmacology/Toxicology
12/20/2006	460	Information Amendment - Pharmacology/Toxicology
12/20/2006	461	IND Safety Report
12/22/2006	462	IND Safety Report
12/27/2006	463	IND Safety Report
1/2/2007	464	IND Safety Report
1/4/2007	465	General Correspondence
1/5/2007	466	IND Safety Report
1/5/2007	467	Protocol Amendment - Change in Protocol TMC125-C206 & TMC125-C216
1/5/2007	468	Information Amendment - Pharmacology/Toxicology
1/8/2007	469	IND Safety Report
1/9/2007	470	IND Safety Report
1/9/2007	471	Information Amendment - Pharmacology/Toxicology
1/10/2007	472	Information Amendment - Pharmacology/Toxicology
1/10/2007	473	General Correspondence
1/11/2007	474	General Correspondence
1/11/2007	475	Information Amendment - Pharmacology/Toxicology
1/12/2007	476	Information Amendment - Pharmacology/Toxicology
1/15/2007	477	Information Amendment - Pharmacology/Toxicology
1/16/2007	478	Information Amendment - Pharmacology/Toxicology
1/17/2007	479	IND Safety Report
1/19/2007	480	IND Safety Report
1/19/2007	481	Protocol Amendment - Change in Protocol TMC125-C217
1/22/2007	482	IND Safety Report
1/22/2007	483	Protocol Amendment - New Investigator TMC125-C216
1/23/2007	484	Response to FDA Request for Information
1/23/2007	485	IND Safety Report
1/24/2007	486	IND Safety Report
1/26/2007	487	IND Safety Report
1/26/2007	488	Annual Report
1/29/2007	489	IND Safety Report
1/30/2007	490	IND Safety Report
1/30/2007	491	Information Amendment - Clinical
1/31/2007	492	Information Amendment - Clinical
2/2/2007	493	IND Safety Report
2/5/2007	494	IND Safety Report
2/6/2007	495	IND Safety Report

Date	Serial #	Type of Submission
2/6/2007	496	Investigator's Brochure Addenda 1
2/7/2007	497	IND Safety Report
2/8/2007	498	Response to FDA Request for Information
2/9/2007	499	IND Safety Report
2/12/2007	500	IND Safety Report
2/13/2007	501	IND Safety Report
2/14/2007	502	IND Safety Report
2/20/2007	503	IND Safety Report
2/23/2007	504	IND Safety Report
2/26/2007	505	IND Safety Report
2/27/2007	506	IND Safety Report
2/28/2007	507	IND Safety Report
3/1/2007	508	Information Amendment - Clinical
3/2/2007	509	Response to FDA Request for Information
3/5/2007	510	IND Safety Report
3/5/2007	511	Information Amendment - Pharmacology/Toxicology
3/5/2007	512	Response to FDA Request for Information
3/7/2007	513	Response to FDA Request for Information
3/8/2007	514	IND Safety Report
3/9/2007	515	IND Safety Report
3/14/2007	516	Information Amendment - Pharmacology/Toxicology
3/15/2007	517	IND Safety Report
3/19/2007	518	IND Safety Report
3/19/2007	519	Response to FDA Request for Information
3/20/2007	520	Protocol Amendment - New Protocol TMC125HIV3009
3/22/2007	521	IND Safety Report
3/22/2007	522	Information Amendment - Chemistry/Microbiology
3/23/2007	523	Meeting Request
3/26/2007	524	IND Safety Report
3/26/2007	525	Information Amendment - Pharmacology/Toxicology
3/28/2007	526	IND Safety Report
3/29/2007	527	Protocol Amendment - New Protocol TMC125-C182
3/30/2007	528	IND Safety Report
3/30/2007	529	Investigator Brochure Addenda
4/3/2007	530	IND Safety Report
4/4/2007	531	Information Amendment - Clinical
4/4/2007	532	Information Amendment - Chemistry/Microbiology
4/4/2007	533	General Correspondence
4/5/2007	534	IND Safety Report
4/6/2007	535	IND Safety Report
4/6/2007	536	IND Safety Report
4/12/2007	537	IND Safety Report

Date	Serial #	Type of Submission
4/16/2007	538	IND Safety Report
4/17/2007	539	IND Safety Report
4/23/2007	540	IND Safety Report
4/24/2007	541	Information Amendment - Clinical
4/25/2007	542	IND Safety Report
4/27/2007	543	Briefing Package Type C Meeting
4/30/2007	544	IND Safety Report
5/3/2007	545	Letter of Authorization - Dr. Bork
5/7/2007	546	IND Safety Report
5/7/2007	547	Tradename Consultation
5/14/2007	548	IND Safety Report
5/16/2007	549	IND Safety Report
5/18/2007	550	IND Safety Report
5/22/2007	551	IND Safety Report
5/23/2007	552	General Correspondence
5/25/2007	553	IND Safety Report
5/29/2007	554	IND Safety Report
5/30/2007	555	IND Safety Report
5/30/2007	556	Information Amendment - Chemistry/Microbiology
6/4/2007	557	IND Safety Report
6/7/2007	558	IND Safety Report
6/11/2007	559	IND Safety Report
6/11/2007	560	IND Safety Report
6/12/2007	561	IND Safety Report
6/19/2007	562	IND Safety Report
6/21/2007	563	IND Safety Report
6/25/2007	564	IND Safety Report
6/26/2007	565	General Correspondence
6/26/2007	566	IND Safety Report
6/28/2007	567	IND Safety Report
7/2/2007	568	IND Safety Report
7/10/2007	569	IND Safety Report
7/13/2007	570	IND Safety Report
7/13/2007	571	General Correspondence
7/16/2007	572	IND Safety Report
7/16/2007	573	IND Safety Report
7/18/2007	574	IND Safety Report
7/18/2007	575	IND Safety Report
7/20/2007	576	IND Safety Report
7/23/2007	577	IND Safety Report
7/24/2007	578	IND Safety Report
7/26/2007	579	IND Safety Report

Date	Serial #	Type of Submission
7/30/2007	580	IND Safety Report
7/30/2007	581	IND Safety Report
7/31/2007	582	IND Safety Report
8/1/2007	583	General Correspondence - Letter of Authorization for Cross-Reference
8/1/2007	584	Letter of Authorization - Dr. Hendersen
8/3/2007	585	Protocol Amendment - New Protocol TMC125HIV2032
8/7/2007	586	IND Safety Report
8/8/2007	587	IND Safety Report
8/9/2007	588	Protocol Amendment-New Protocol TMC125-C126
8/13/2007	589	IND Safety Report
8/13/2007	590	IND Safety Report
8/14/2007	591	Letter of Authorization - Dr. Koepe
8/14/2007	592	IND Safety Report
8/16/2007	593	IND Safety Report
8/17/2007	594	IND Safety Report
8/20/2007	595	IND Safety Report
8/21/2007	596	IND Safety Report
8/23/2007	597	IND Safety Report
8/24/2007	598	IND Safety Report
8/27/2007	599	IND Safety Report
8/28/2007	600	IND Safety Report
8/29/2007	601	IND Safety Report
8/31/2007	602	IND Safety Report
9/4/2007	603	General Correspondence - Letter of Authorization
9/4/2007	604	IND Safety Report
9/5/2007	605	IND Safety Report
9/6/2007	606	IND Safety Report
9/7/2007	607	IND Safety Report
9/10/2007	608	IND Safety Report
9/10/2007	609	IND Safety Report
9/10/2007	610	General Correspondence
9/11/2007	611	Information Amendment - Clinical
9/12/2007	612	IND Safety Report
9/13/2007	613	IND Safety Report
9/14/2007	614	Investigator's Brochure Edition 12
9/17/2007	615	General Correspondence - Letter of Authorization
9/19/2007	616	IND Safety Report
9/19/2007	617	IND Safety Report
9/20/2007	618	IND Safety Report
9/24/2007	619	IND Safety Report
9/25/2007	620	IND Safety Report
9/26/2007	621	IND Safety Report

Date	Serial #	Type of Submission
9/27/2007	622	IND Safety Report
10/1/2007	623	IND Safety Report
10/1/2007	624	IND Safety Report
10/2/2007	625	IND Safety Report
10/3/2007	626	IND Safety Report
10/4/2007	627	IND Safety Report
10/4/2007	628	IND Safety Report
10/5/2007	629	Proposed Pediatric Study Request
10/5/2007	630	Draft Protocol for Review
10/8/2007	631	IND Safety Report
10/10/2007	632	IND Safety Report
10/11/2007	633	Information Amendment - Clinical
10/15/2007	634	IND Safety Report
10/17/2007	635	IND Safety Report
10/17/2007	636	Protocol Amendment - New Investigator TMC125-C126
10/22/2007	637	IND Safety Report
10/24/2007	638	IND Safety Report
10/25/2007	639	IND Safety Report
10/26/2007	640	IND Safety Report
10/29/2007	641	IND Safety Report
10/30/2007	642	IND Safety Report
10/31/2007	643	IND Safety Report
10/31/2007	644	Information Amendment - Pharmacology/Toxicology
11/2/2007	645	IND Safety Report
11/2/2007	646	Protocol Amendment - Change in Protocol TMC125-C206 & TMC125-C216
11/5/2007	647	IND Safety Report
11/6/2007	648	IND Safety Report
11/7/2007	649	IND Safety Report
11/12/2007	650	IND Safety Report
11/13/2007	651	IND Safety Report
11/14/2007	652	Information Amendment - Pharmacology/Toxicology
11/14/2007	653	IND Safety Report
11/16/2007	654	IND Safety Report
11/19/2007	656	IND Safety Report
11/19/2007	657	IND Safety Report
11/20/2007	658	IND Safety Report
11/21/2007	659	IND Safety Report
11/22/2007	660	IND Safety Report
11/23/2007	661	IND Safety Report
11/26/2007	662	IND Safety Report
11/28/2007	663	IND Safety Report
11/29/2007	664	IND Safety Report

Date	Serial #	Type of Submission
11/29/2007	665	Protocol Amendment - New Investigator TMC125HIV2032
11/30/2007	666	IND Safety Report
12/3/2007	667	IND Safety Report
12/4/2007	668	IND Safety Report
1/4/2008	689	Protocol Amendment - Change in Protocol
1/7/2008	690	IND Safety Report
1/8/2008	691	IND Safety Report
1/9/2008	692	IND Safety Report
1/11/2008	693	IND Safety Report
1/16/2008	694	IND Safety Report
1/17/2008	695	IND Safety Report
1/17/2008	696	Information Amendment - Clinical
1/18/2008	697	IND Safety Report
1/18/2008	698	General Correspondence- Response to Request for Information
1/22/2008	699	IND Safety Report

NDA 22-187 (INTELENCE™ (etravirine)) US eCTD Submission Log

Date	Submission
June 4, 2007	NDA Submission
July 6, 2007	NDA Resubmission of CMC section
July 17, 2007	NDA Submission
August 3, 2007	Response to FDA Request for Information
September 4, 2007	Response to FDA Request for Information
September 7, 2007	Response to FDA Request for Information
October 4, 2007	NDA Safety Update & Amendment to a Pending Application
October 24, 2007	Response to FDA Request for Information
October 30, 2007	Response to FDA Request for Information
December 3, 2007	Response to FDA Request for Information
December 14, 2007	Response to FDA Request for Information
January 4, 2008	Response to FDA Request for Information
January 15, 2008	Response to FDA Request for Information
January 16, 2008	Amendment to a Pending Application
January 17, 2008	Amendment to a Pending Application

Exhibit 9

STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION AND LENGTH OF EXTENSION CLAIMED

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 7,037,917 Issued: May 2, 2006
Expiration Date: November 5, 2019

Inventors: Bart De Corte; Marc Rene De Jonge; Jan Heeres; Chih Yung Ho; Paul Adriaan Jan Janssen; Robert W. Kavash; Lucien Maria Henricus Koymans; Michael Joseph Kukla; Donald William Ludovici; Koen Jeanne Alfons Van Aken; Koenraad Jozef Lodewijk Marcel Andries

Title: HIV REPLICATION INHIBITING PYRIMIDINES

Statement of Eligibility for Extension of Patent Term Due to Regulatory Review

I, Laura A. Donnelly, represent that I am the attorney of record duly appointed by the assignee of the entire right, title and interest in the patent application identified above, and do state on behalf of the Applicant as follows:

To the best of my knowledge, U.S. Patent No. 7,037,917 (the '917 Patent) meets all of the eligibility criteria set forth in 37 C.F.R §§1.710 and 1.720 for extension of patent term.

The '917 Patent claims a "product" (and a method of using a product) as that term is defined in 37 C.F.R §1.710, specifically the active ingredient, etravirine, of a new human drug, INTELENCE™. 37 C.F.R §1.720(a).

The term of the '917 Patent has never been previously extended. 37 C.F.R §1.720(b).

An application for extension of the term of the '917 Patent in compliance with 37 C.F.R §1.740 is herewith submitted. 37 C.F.R §1.720(c).

The approved product, INTELENCE™, has been subject to a regulatory review period as defined in 35 U.S.C. §156(g) before its commercial marketing or use. 37 C.F.R §1.720(d).

The approved product, INTELENCE™, has received permission for commercial marketing or use and the permission for the commercial marketing or use of the product is the first received permission for commercial marketing or use under the provision of law under which the applicable regulatory review occurred. 37 C.F.R §1.720(e).

The application for extension of the term of the '917 Patent submitted herewith is submitted within the sixty-day period beginning on the date the product first received permission for commercial marketing or use under the provisions of law under which the applicable regulatory review period occurred. 37 C.F.R §1.720(f).

The term of the '917 Patent, including any interim extension issued pursuant to § 1.790, has not expired before the submission of an application in compliance with 37 C.F.R. § 1.741. 37 C.F.R §1.720(g).

No other patent term has been extended for the same regulatory review period for the approved product, INTELENCE™. 37 C.F.R §1.720(h).

The extension claimed is 404 days, setting the patent to expire on December 13, 2020. The following are the calculations, made in accordance with 37 C.F.R. § 1.775, that result in the claimed extension:

(1) The testing phase began on December 27, 2001 (the effective date of the IND) and ended on July 17, 2007 (the submission date of the NDA).

(2) The approval phase began on July 18, 2007 (the day of receipt by the FDA of the NDA) and approval was granted on January 18, 2008.

(3) The total number of days in the testing phase (from and including December 27, 2001 to and including July 17, 2007) is 2,028 days from the start date to the end date, end date included. One half of the testing phase is 1,014 days.

(4) The total number of days in the approval phase is (from and including July 18, 2007 to and including January 18, 2008) is 184 days from the start date to the end date, end date included.

(5) The patent issued on May 2, 2006, while INTELENCE™ was in the testing phase of regulatory review. Pursuant to 35 U.S.C. 156(c), only that portion of the regulatory review period occurring after the date the patent has issued can be considered in a determination of patent term extension. Pursuant to 37 C.F.R. § 1.775(d)(1), the number of days in the testing phase (2028) is reduced by the number of days which occurred on or before the date on which the patent issued (i.e., the number of days between December 27, 2001 and May 2, 2006) (1587) to arrive at 441 days). One half of the testing phase is 220.

(6) Applicant acted with due diligence throughout the entire regulatory review period.

(7) The sum of the (a) number of days in one half of the testing phase available for the calculcation in the testing phase (220), and (b) number of days in the approval phase (184) is: 404 days.

(8) The original expiration date of the patent is November 5, 2019.

(9) Addition of the extension of 404 days to the original expiration date of the patent extends the expiration date of the patent to December 13, 2020.

(10) Fourteen years from the approval date of the product (January 18, 2008) is January 18, 2022.

(11) Pursuant to 35 U.S.C. §156(c)(3), the extended term of the patent cannot exceed 14 years from the date of product approval. The fourteen year cap does not apply since the extension of 404 days sets the patent to expire on December 13, 2020, which is before the date that is 14 years post-approval (January 18, 2022).

(12) Pursuant to 35 U.S.C. §156(g)(6)(A), the extension period is subject to a five year limitation (for patents issued after September 24, 1984). The five year limitation does not apply since the extension of 404 days is less than five years.

(13) In light of the conclusions set forth above, the extended expiration date of the '917 Patent is believed to be December 13, 2020.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: March 10, 2008

Laura A. Donnelly
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933 U.S.A.

Reg. No.: 38,435
Tel. No.: 732-524-1729
Customer No.: 000027777